Summary of Safety and Effectiveness Data

I. General Information

Product Generic Name:	Drug-Eluting Coronary Stent System (NIQ)
Product Trade Name:	Endeavor Zotarolimus-Eluting Coronary Stent on the Over-the-Wire (OTW), Rapid Exchange (RX), or Multi-Exchange II (MX^2) Stent Delivery Systems
Applicant's Name and Address:	Medtronic Vascular 3576 Unocal Place Santa Rosa, CA 95403
Premarket Approval Application (PMA) Number:	P060033
Date of Panel Recommendation:	October 10, 2007
Date of Notice of Approval to Applicant:	February 1, 2008

II. Indications For Use

The Endeavor Zotarolimus-Eluting Coronary Stent System (hereafter referred to as the Endeavor stent system) is indicated for improving coronary luminal diameter in patients with ischemic heart disease due to *de novo* lesions of length ≤ 27 mm in native coronary arteries with reference vessel diameters of ≥ 2.5 mm to ≤ 3.5 mm.

III. Contraindications

The Endeavor Zotarolimus-Eluting Coronary Stent System is contraindicated for use in patients with:

- Known hypersensitivity to zotarolimus or structurally-related compounds.
- Known hypersensitivity to the cobalt-based alloy (cobalt, nickel, chromium, and molybdenum).
- Known hypersensitivity to the Phosphorylcholine polymer or its individual components (see Section V. B – 2. Inactive Ingredients for details).

Coronary artery stenting is contraindicated for use in:

- Patients who cannot receive recommended anti-platelet and/or anticoagulant therapy.
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or delivery device.

IV. Warnings and Precautions

The warnings and precautions can be found in the Endeavor Zotarolimus-Eluting Coronary Stent System labeling.

V. Device Description

The Endeavor Zotarolimus-Eluting Coronary Stent System is a device/drug combination product comprised of device components (Driver™ Coronary Stent and Micro-Driver™ Coronary Stent and the Endeavor delivery systems) and a drug component (a formulation of zotarolimus contained in a polymer coating). The characteristics of the Endeavor Zotarolimus-Eluting Coronary Stent System are described in Table 1.

Table 1: The Endeavor Zotarolimus-Eluting Coronary Stent System Product Description

	Endeavor Rapid Exchange (RX) Delivery System	Endeavor Over-The-Wire (OTW) Delivery System	Endeavor Multi-Exchange II (MX^2) Delivery System
Available Stent lengths (mm)*	8, 9, 12, 14, 15, 18, 24, 30		
Available Stent diameters (mm)**	2.5, 3.0, 3.5		
Stent Material	A cobalt-based alloy (MP35N) – the Driver and Micro-Driver stents		
Drug Component	A spray coating of polymer carrier loaded with zotarolimus is applied to the stent at a drug loading of 10 µg/mm stent length. The maximum nominal drug content on the longest stent (30 mm) is 300 µg.		
Delivery System Working Length (cm)	135	135	138
Delivery System Adapter Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 25 cm from tip. Designed for guidewire ≤ 0.014".	Y-Connector (side arm for access to balloon inflation/ deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤ 0.014".	Single access port to inflation lumen. Guidewire exits through a Z-component located on the proximal shaft. Designed for guidewire ≤ 0.014".
Stent Delivery Balloon	A semi-compliant balloon mounted on the distal end of the catheter to facilitate stent deployment. There are proximal and distal pillows formed on either side of the stent which aid in holding the stent in position. Two radiopaque balloon markers are located on the distal section of the inner member and are positioned to mark the working length of the balloon.		
Balloon Inflation Pressure	Nominal Inflation Pressure: 9 ATM Rated Burst Inflation Pressure: 16 ATM		
Guiding Catheter Compatibility	0.056" minimum (5 F)	0.056" minimum (5 F)	0.064" minimum (6 F)
Distal Section Outer Diameter	Distal = 2.7 F	Distal = 2.7 F	Distal = 2.7 F
	Proximal = 3.0 F	Proximal = 3.0 F	Middle = 3.0 F
			Proximal = 3.8 F
Proximal Outer Diameter	2.2 F	3.3 F	2.3 F x 4.2 F (Oval)

* 2.5 mm diameter stents are not available in 9 and 15 mm lengths
** 3.0 and 3.5 mm diameter stents are not available in 8 and 14 mm lengths

A. Device Component Description

The device component consists of the Driver™ Coronary Stent or Micro-Driver™ Coronary Stent pre-mounted onto one of three delivery systems; Over-The-Wire (OTW), Rapid Exchange (RX) or Multi-Exchange II (MX^2) Delivery Systems. Each delivery system provides a means for delivering the stent through the coronary vasculature and, once in the desired location, expands the stent through balloon inflation. The delivery systems utilized for the Endeavor product are similar in materials, design and construction to the approved Driver (P030009, approved October 1, 2003; Driver MX^2 P030009/S001, approved on August 4, 2004; Driver RX, P030009/S003, approved on December 22, 2005) and Micro-Driver (P030009/S002, approved on April 21, 2006) delivery systems.

The Endeavor stent is made of the cobalt alloy MP35N conforming to ASTM F562. The modular stent segments are created from a single ring formed into a repeating pattern of crowns and struts. The appropriate ring is formed into alternating upper and lower crowns with seven (2.5 mm diameters) or ten (3.0 – 3.5 mm diameters) crowns per end, connected by axial struts in a sinusoidal pattern. The stent is crimped onto various size delivery catheter balloons, with diameters of 2.5 mm, 3.0 mm or 3.5 mm.

The Endeavor stent contains 10 μg zotarolimus per millimeter of stent length for all diameters. Because an identical dose (10μg/mm zotarolimus per mm stent length) is used for the entire Endeavor 2.5 mm – 3.5 mm diameter range, the total drug per stent is a function of stent length, irrespective of stent diameter.

B. Drug Component Description

The drug component of the Endeavor Zotarolimus-Eluting Coronary Stent System consists of zotarolimus (the active ingredient) and Phosphorylcholine (PC) polymer (the inactive ingredient).

A. 1. Zotarolimus

The active pharmaceutical ingredient utilized in the Endeavor stent is zotarolimus. It is a tetrazole-containing macrocyclic immunosuppressant. The chemical name of zotarolimus is: [3S-[3R*[S*(1R*,3S*,4R*)],6S*,7E,9S*,10S*,12S*,14R*,15E,17E, 19E,21R*,23R*, 26S*,27S*,34aR*]]-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[2-[3-methoxy-4-(1H-tetrazoyl-1-yl)cyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c] [1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone.

The chemical structure of zotarolimus is shown below (Figure 1).

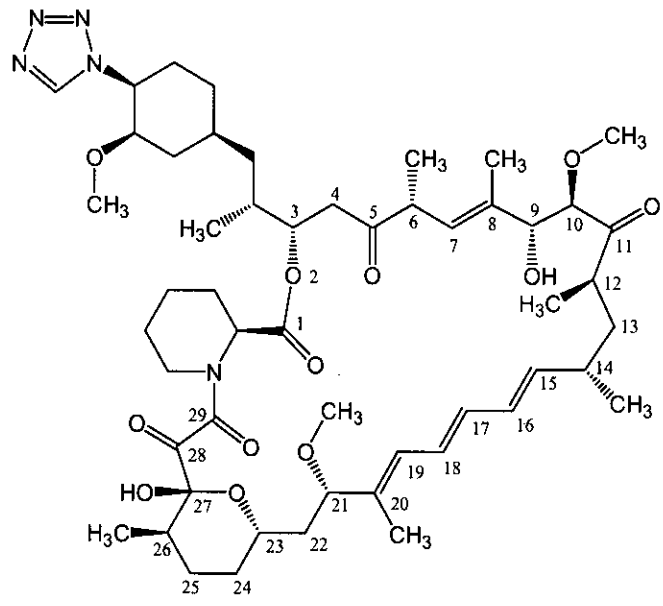


Figure 1: Chemical Structure of Zotarolimus

Zotarolimus has extremely low water solubility and is a lipophilic compound that is freely soluble in propylene glycol, acetone, toluene, acetonitrile, ethanol, benzyl alcohol and dimethyl sulfoxide (DMSO). The molecular formula of zotarolimus is $C_{52}H_{79}N_5O_{12}$ and its molecular weight is 966.2.

Zotarolimus does not have any ionizable groups in the physiological pH range; therefore, its solubility is expected to be unaltered in this range.

B. 2. Inactive Ingredients

The only inactive ingredient in the Endeavor stent is the Phosphorylcholine (PC) polymer, which acts as a carrier for zotarolimus. The PC polymer consists of 2-methacryloyloxyethyl phosphorylcholine that is synthesized and then used in the preparation of cross-linked polymer membranes with lauryl methacrylate, hydroxypropyl methacrylate and trimethoxysilylpropyl methacrylate (crosslinker) co-monomers.

The molecular weight of PC polymer was estimated using viscometry and resulted in values of Mw ranging from 160,000 to 270,000. These figures were supported by light scattering values of Mw (g/mol) ranging from 100,000 to 200,000.

PC polymer in a solvent carrier (ethanol) is applied to the Driver stent to form the base layer coat of the Endeavor stent. The polymer is also mixed with the drug zotarolimus and then applied to the base layer-coated stents. Finally, a drug-free overspray of PC polymer is applied after the stent has been coated with the drug/polymer formulation and it has been crimped onto the balloon. The drug/polymer coating is applied to the entire surface (i.e., luminal and abluminal) of the stent. The structural formula of the polymer is shown in Figure 2.

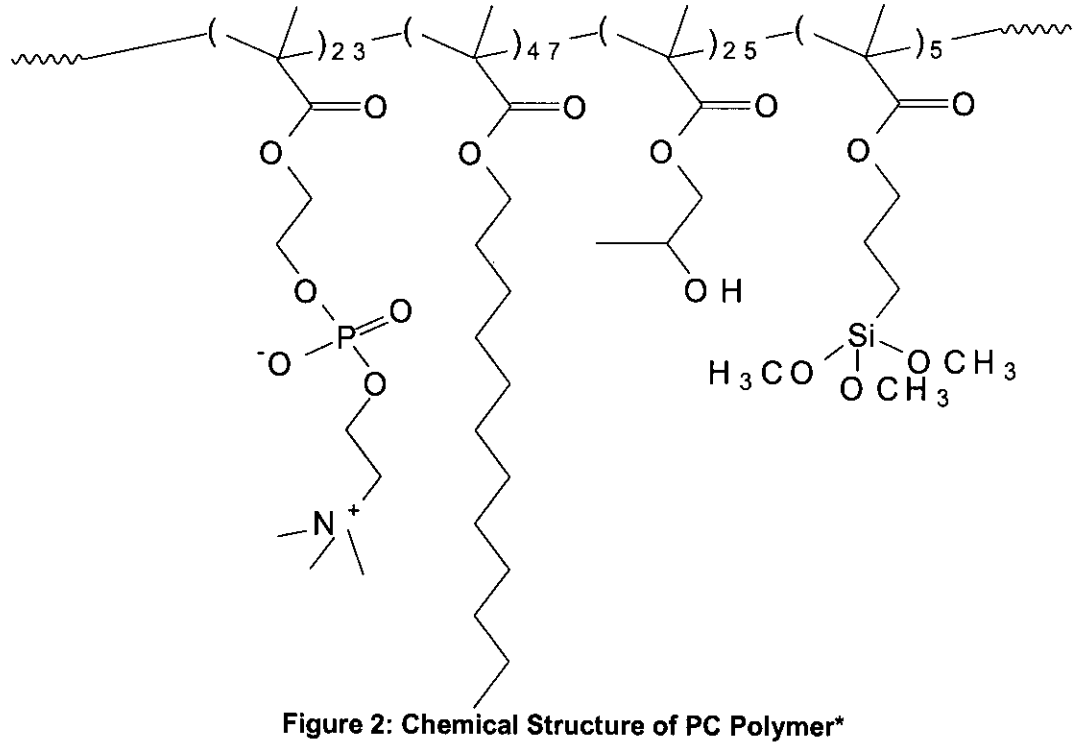


Figure 2: Chemical Structure of PC Polymer*

* PC Technology™ is licensed under patents or patent applications owned by Biocompatibles.

Table 2: Endeavor Zotarolimus-Eluting Coronary Stent System Product Matrix and Nominal Zotarolimus Doses

Product Number OTW	Product Number RX	Product Number MX[2]	Nominal Expanded Stent ID (mm)	Nominal Unexpanded Stent Length (mm)	Nominal Zotarolimus Content (µg)
EN25008W	EN25008UX	EN25008MX	2.50	8*	84
EN30009W	EN30009UX	EN30009MX	3.00	9	90
EN35009W	EN35009UX	EN35009MX	3.50	9	90
EN25012W	EN25012UX	EN25012MX	2.50	12	120
EN30012W	EN30012UX	EN30012MX	3.00	12	120
EN35012W	EN35012UX	EN35012MX	3.50	12	120
EN25014W	EN25014UX	EN25014MX	2.50	14*	144
EN30015W	EN30015UX	EN30015MX	3.00	15	150
EN35015W	EN35015UX	EN35015MX	3.50	15	150
EN25018W	EN25018UX	EN25018MX	2.50	18	180
EN30018W	EN30018UX	EN30018MX	3.00	18	180
EN35018W	EN35018UX	EN35018MX	3.50	18	180
EN25024W	EN25024UX	EN25024MX	2.50	24	240
EN30024W	EN30024UX	EN30024MX	3.00	24	240
EN35024W	EN35024UX	EN35024MX	3.50	24	240
EN25030W	EN25030UX	EN25030MX	2.50	30	300
EN30030W	EN30030UX	EN30030MX	3.00	30	300
EN35030W	EN35030UX	EN35030MX	3.50	30	300

* *Note*:
The 8 mm and 14 mm stent lengths have a total nominal drug content of 84 µg and 144 µg, respectively, since the actual stent length for the 8 mm stent is 8.4 mm, and the actual stent length for the 14 mm stent is 14.4 mm.

C. Mechanism of Action

The mechanism (or mechanisms) by which the Endeavor Zotarolimus-Eluting Coronary Stent System affects neointimal production as seen in clinical studies has not been established conclusively. *In vitro*, zotarolimus inhibited growth factor-induced proliferation of human coronary artery smooth muscle cells and also demonstrated binding affinity with FKBP12 (binding protein). The suggested mechanism of action of zotarolimus is to bind to FKBP12, leading to the formation of a trimeric complex with the protein kinase mTOR (mammalian target of rapamycin), inhibiting its activity. Inhibition of mTOR activity leads to inhibition of cell cycle progression from the G1 to the S phase.

VI. Alternative Practices and Procedures

Treatment of patients with coronary artery disease may include exercise, diet, drug therapy, percutaneous coronary interventions (such as angioplasty, bare metal stents. coated stents, and other drug-eluting stents), and coronary artery bypass surgery (CABG).

VII. Marketing History

The Endeavor Zotarolimus-Eluting Coronary Stent System is commercially available in the following countries:

• Albania	• Brazil	• Germany	• Lebanon	• Pakistan	• Sudan
• Algeria	• Bulgaria	• Ghana	• Libya	• Panama	• Sweden
• Antigua and Barbuda	• Cayman Islands	• Greece	• Liechtenstein	• Paraguay	• Switzerland
• Argentina	• Chile	• Guatemala	• Lithuania	• Peru	• Syria
• Armenia	• China	• Honduras	• Luxembourg	• Poland	• Thailand
• Aruba	• Colombia	• Hong Kong	• Malaysia	• Portugal	• Trinidad and Tobago
• Australia	• Costa Rica	• Hungary	• Malta	• Qatar	• Tunisia
• Austria	• Cyprus	• Iceland	• Mauritius	• Romania	• Turkey
• Bahamas	• Czech Republic	• India	• Mexico	• Russia	• Uganda
• Bahrain	• Denmark	• Iran	• Morocco	• Saudi Arabia	• United Arab Emirates
• Bangladesh	• Dominican Republic	• Ireland	• Mozambique	• Senegal	• United Kingdom
• Barbados	• Ecuador	• Israel	• Nepal	• Serbia & Montenegro	• Uruguay
• Belgium	• Egypt	• Italy	• Netherlands	• Singapore	• Venezuela
• Belize	• El Salvador	• Jamaica	• New Zealand	• Slovakia	• Virginia Islands (British)
• Bermuda	• Estonia	• Jordan	• Nicaragua	• Slovenia	• Yemen
• Bolivia	• Finland	• Kenya	• Nigeria	• South Africa	• Zimbabwe
• Bosnia-Herzegovina	• France	• Kuwait	• Norway	• South Korea	
• Botswana	• Georgia	• Latvia	• Oman	• Spain	

As of December 31, 2007, approximately 392,000 Endeavor Zotarolimus-Eluting Coronary Stent Systems have been distributed outside of the United States (OUS). No products have been withdrawn from the market in any country for any reason.

VIII. Summary of Non-Clinical Studies

A series of non-clinical laboratory studies were performed, pertaining to the stent and the stent delivery system (i.e., the stent mounted on either the Endeavor OTW, RX and MX^2 stent delivery system), the polymer substance (i.e., Phosphorylcholine), the drug substance (i.e., zotarolimus), and the finished combination product (i.e., Endeavor Zotarolimus-Eluting Coronary Stent System).

A. Studies of the Drug Substance

Medtronic Vascular provided a letter from the drug substance manufacturer, Abbott Laboratories Inc., authorizing FDA access to a Drug Master File (DMF) in support of this application. *In vivo* and *in vitro* pharmacology and toxicology studies as well as animal and human pharmacokinetic studies were conducted on zotarolimus to provide information about systemic and regional toxicity, distribution profiles, end-organ disposition, drug metabolism and potential drug-drug interactions.

1. Safety Pharmacology

Safety pharmacology studies have been conducted to determine the effects of zotarolimus on the central nervous system and pulmonary function in rats, the cardiovascular system in conscious primates, hemodynamic and electrophysiologic function in conscious and anesthetized dogs, canine cardiac Purkinje fibers repolarization (*in vitro* assay), hERG current (*in vitro*), antigenicity in guinea pigs, and lymph nodes in mice.

IV administered zotarolimus has no effect on the CNS and respiratory system parameters in the rat at blood concentrations of ~ 30-times the estimated C_{max} (maximum blood concentration) from one stent. In the anesthetized dog model, IV doses of zotarolimus showed no significant effect on heart rate, QTc and PR interval. The blood concentration of zotarolimus is estimated to be about 5-fold higher than the C_{max} obtained in the highest IV dose tested in human multiple dose study for safety (800 μg for 14 days). Zotarolimus did not reduce hERG current at concentration up to 181 ng/ml (72 times the estimated clinical C_{max}). Zotarolimus showed minimal prolongation of the Purkinje fiber action potential duration (by 6%) at concentration up to 21 ng/ml (9 times estimated clinical C_{max}).

Zotarolimus caused *in vitro* inhibition of cell proliferation of human T cell, coronary artery smooth muscle and endothelial cells at IC_{50} of 1.2, 2.9 and 2.6 nM, respectively. Zotarolimus did not exhibit receptor interaction when tested *in vitro* at a concentration of 10 μM for binding to 73 individual assays. At levels of 200 ng/ml (100-fold greater than a typical projected C_{max} of 1.8 ng/ml), zotarolimus caused no direct aggregation of human platelets in whole blood or did not enhance aggregation to stimulation by platelet agonists.

In guinea pigs sensitized once per week for four weeks by subcutaneous administration of zotarolimus (30 μg/kg), showed no induced systemic anaphylactic or passive cutaneous anaphylactic reactions indicating that zotarolimus was non-antigenic. Topically applied zotarolimus (50% w/v) on the dorsal surface of both ears of mice showed no increase in

^{3}H-thymidine incorporation in the lymph nodes indicating lack of skin sensitizing activity.

2. Toxicology

Toxicology studies have been conducted to determine the general toxicological effects in various species and the potential for genetic, reproductive and developmental toxicology. These include single and 28 day repeat dose IV infusion toxicokinetic studies in the rat and cynomolgus monkey, fertility and teratology reproductive toxicity studies in the rat and rabbit, and genotoxicity studies *in vitro* and in the mouse.

Zotarolimus was embryo/feto-toxic in rats at IV dosages of 25 µg/kg/day and above (approximately 3 times the cumulative blood exposure provided by Endeavor stents coated with 300 µg zotarolimus). Embryotoxicity was manifested as reduced fetal body weights and fetal ossification delays, but no major fetal malformations, deaths, or minor fetal abnormalities were observed. No embryo-fetal effects were observed in pregnant rabbits at the maternally toxic dosage of 30 µg/kg/day (approximately 13 times the cumulative blood exposure provided by Endeavor stents coated with 300 µg zotarolimus). The Endeavor stent should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo/fetus.

Zotarolimus was not genotoxic in the *in vitro* bacterial reverse mutation assay, the human peripheral lymphocyte chromosomal aberration assay, or the *in vivo* mouse micronucleus assay.

3. Absorption, Distribution, Metabolism, and Excretion (ADME) Studies

Studies were conducted to characterize the absorption, distribution, metabolism, and excretion profiles in various species.

Absorption studies included pharmacokinetic evaluations in the rat, rabbit, mouse, monkey, and pig following single IV or oral drug dosing.

Distribution studies included *in vitro* distribution in human whole blood, *in vitro* binding to plasma proteins in the mouse, rat, rabbit, dog, pig, monkey, and human plasma, and tracing of radioactivity-labeled drug in the rat, monkey, and pig following IV dosing. The results of the plasma protein binding study suggest that all clinically relevant concentrations, zotarolimus would be extensively protein bound in plasma and would undergo significant degradation. Results from the analysis of radioactive-labeled drug in the blood and plasma are consistent with zotarolimus undergoing rapid degradation within plasma while drug that is sequestered within blood cells is relatively more stable and is released slowly. All concentrations largely decreased in parallel with blood radioactivity with little evidence for accumulation.

Metabolism studies included analysis of metabolites after metabolism by human liver microsomes *in vitro*, analysis of metabolites in blood, plasma, feces, and urine in the rat, pig, monkey, and human following IV dosing, metabolism and excretion in rats,

metabolism, excretion, and tissue distribution in rabbits, metabolism by hepatocytes from the rat, dog, monkey, and human, and the effect of ketoconazole on PK profile in the dog following IV dosing. Review of studies of the metabolism in the rat, dog, monkey, and human indicated that in all cases the presence of hepatocytes accelerated the loss of parent compound from the incubation mixture. Although no metabolites or breakdown products were formally identified in the present study, it is likely that many routes of metabolism will be shared.

In the studies of metabolites by human liver microsomes, the IC_{50} for zotarolimus determined as a competitive inhibitor was not significantly different from the potency determined after pre-incubation, suggesting that the compound is not a mechanism-based inhibitor of human CYP3A enzymes. The anticipated clinical plasma levels of zotarolimus are unlikely to exceed the IC_{50} values determined in this study, which would suggest that the compound is unlikely to be a source of clinical drug–drug interactions through inhibition of CYP3A.

In studies of the effects of zotarolimus on seven cytochrome P450-dependent monooxygenase activities in human liver microsomes, in all cases the extent of inhibition of each enzyme were largely the same, irrespective of the absence or presence of a pre-incubation step, suggesting that the compound is not a mechanism based inhibitor of any of the human P450 enzymes tested. Given the anticipated clinical plasma levels of zotarolimus, the compound is unlikely to be a source of clinical drug-drug interactions through inhibition of CYP3A or the other P450 enzymes tested. In common with other immunosuppressive macrolides, such as sirolimus, the metabolism of zotarolimus appears to be catalyzed by cytochromes P450 of the CYP3A subfamily, CYP3A4 in particular.

In a study of ketoconazole interaction with zotarolimus in the dog, the results indicated that oxidative metabolism of zotarolimus can be blocked by the CYP3A selective inhibitor ketoconazole. Co-dosing with ketoconazole produced a statistically significant ($p < 0.05$) increase in the zotarolimus area under the curve, with a significant decrease in the clearance values.

Excretion studies in male rats included assessment of physical and metabolic stability in excreta. The results indicated that elimination occurs primarily via the feces.

4. Intravenous Administration of Zotarolimus

- Pharmacokinetics

Zotarolimus pharmacokinetic activity has been determined following intravenous (IV) administration in healthy patients. Table 3 provides a summary of the pharmacokinetic analysis.

Table 3: Pharmacokinetic Parameters (Mean ± standard deviation) in Patients Following Intravenous Administration of Zotarolimus

PK Parameters	Units	200 µg QD (N = 15)		400 µg QD (N = 16)		800 µg QD (N = 16)	
		Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
C_{max}	(ng/mL)	11.41 ± 1.38¥	11.93 ± 1.25	21.99 ± 3.79	23.31 ± 3.15	37.72 ± 7.00	41.79 ± 6.68
T_{max}	(h)	1.05 ± 0.04¥	1.03 ± 0.04	1.00 ± 0.14	1.05 ± 0.04	1.03 ± 0.04	1.03 ± 0.05
AUC_{0-24}	(ng•h/mL)	34.19 ± 4.39¥	47.70 ± 6.68	68.43 ± 15.41	100.47 ± 18.02	123.48 ± 13.34	174.43 ± 19.88
$t_{1/2}$ $	(h)		32.9 ± 6.8		37.6 ± 4.5		36.0 ± 4.7
CL £	(L/h)	4.2 ± 0.6	4.2 ± 0.6	4.0 ± 0.9	4.0 ± 0.9	4.6 ± 0.4	4.6 ± 0.4

¥ N = 16

$ Harmonic mean ± pseudo-standard deviation

£ Clearance data is calculated using compartmental methods. All other data presented in Table 3 is calculated using non-compartmental methods.

When administered intravenously for 14 consecutive days, zotarolimus showed dose proportionality. Renal excretion is not a major route of elimination for zotarolimus, as approximately 0.1% of the dose was excreted as unchanged drug in the urine per day. In multiple doses of 200, 400, and 800 µg, zotarolimus was generally well tolerated by the patients. No clinically significant changes in physical examination, vital signs, or laboratory measurements were observed during the course of the study. For a total stent length of 48 mm (480 µg drug dose), a C_{max} of 4.0 ng/mL and AUC_{0-inf} (area under the blood concentration-time curve (AUC) from time 0 to infinity) of 162 ng•h/mL were estimated as seen in Table 4 below. These calculations are based on the mean C_{max} and AUC_{0-inf} values calculated from the IV dosing studies conducted on zotarolimus.

Table 4: Zotarolimus Dose Exposure

Units	480µg Dose Stent	Exposure Multiples
C_{max} (ng/ml)	4.0	27.69¥
AUC_{0-inf} (ng•h/mL)	162	15.06#

¥ Calculated based on the mean C_{max} value (110.78) from the highest dose group (900 µg) from human single escalation IV dose study conducted on zotarolimus

Based on the mean all day AUC_{0-inf} (Day 1 to 14); 2440 ng•h/mL) value from the highest dose regimen (800 µg QD x 14 days) from human multiple escalation IV dose study conducted on zotarolimus

- Adverse Event Profile

The incidence of adverse events attributed to the drug zotarolimus was determined in IV escalating and multiple-dose studies. In the single-escalating dose study, the proportion of patients reporting treatment-emergent adverse events was slightly lower among patients who received doses of zotarolimus than those who received placebo for zotarolimus. The most common treatment-emergent adverse events associated with zotarolimus were application site reaction, injection site reaction, pain, and hematuria. There were no deaths or other serious adverse events reported in this study. No clinically significant changes in physical examination, vital signs, or laboratory measurements were observed during the course of the study. Table 5 provides a summary of the analysis.

Table 5: Summary of Treatment-Emergent Adverse Events Reported by Two or More Patients in Any One Treatment by Body Systems and Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART Term) in the Single-escalating Dose Study

BODY SYSTEMS	COSTART Term	All Placebo N = 20 (%)	Zotarolimus 100 µg N = 8 (%)	Zotarolimus 300 µg N = 8 (%)	Zotarolimus 500 µg N = 8 (%)	Zotarolimus 700 µg N = 8 (%)	Zotarolimus 900 µg N = 8 (%)
Body as a whole	Headache	3 (15%)	0 (0%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)
	Injection site Reaction	1(5%)	0 (0%)	0 (0%)	3 (38%)	0 (0%)	0 (0%)
	Pain	7 (35%)	1 (13%)	0 (0%)	5 (63%)	5 (63%)	2 (25%)
Digestive System	Diarrhea	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Skin and Appendage	Application site Reaction	8 (40%)	1 (13%)	5 (63%)	2 (25%)	1 (13%)	5 (63%)
Urogenital System	Hematuria	1 (5%)	0 (0%)	1 (13%)	0 (0%)	1 (13%)	1 (13%)

In the multiple-dose study, the proportion of patients reporting treatment-emergent adverse events was similar among patients who received doses of zotarolimus, and the most common treatment-emergent adverse events associated with zotarolimus were headache, pain, injection site reaction, dry skin, abdominal pain, diarrhea, and rash. There were no deaths or other serious adverse events. Results of other safety analyses including individual patient changes, changes over time and individual clinically significant values for vital signs, laboratory safety assessments and physical examinations were unremarkable for each treatment group. No clinically significant changes in physical examination, vital signs, or laboratory measurements were observed during the course of the study. No differences were seen among the doses with respect to adverse event profiles or overall drug safety. Table 6 provides a summary of the analysis.

Table 6: Summary of Treatment-Emergent Adverse Events Reported by Two or More Patients in Any One Treatment by Body Systems and COSTART Term in the Multiple-dose Study

BODY SYSTEM	COSTART Term	All Placebo (N = 16) N (%)	200 µg QD (N = 16) N (%)	400 µg QD (N = 16) N (%)	800 µg QD (N = 16) N (%)
Body as a whole	Headache	1 (4)	2 (13)	2 (13)	2 (13)
	Pain	1 (4)	2 (13)	1 (6)	0 (0)
	Injection Site Reaction	2 (8)	0 (0)	0 (0)	2 (13)
	Injection Site Pain	2 (8)	0 (0)	0 (0)	0 (0)
	Abdominal Pain	1 (4)	1 (6)		0 (0)
Digestive System	Diarrhea	1 (4)	0 (0)	1 (6)	0 (0)
Skin and Appendage	Dry Skin	0 (0)	0 (0)	2 (13)	0 (0)
	Rash	0 (0)	1 (6)	1 (6)	0 (0)

5. *In Vivo* Pharmacokinetics

The Endeavor US Pharmacokinetic (PK) study was conducted to evaluate the pharmacokinetic profile of the Endeavor Zotarolimus-Eluting Coronary Stent System in eligible patients. The Endeavor US PK Registry was a prospective, multi-center, single-arm, open-label study designed to assess the acute pharmacokinetics and safety of zotarolimus administered using the Endeavor Zotarolimus-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries. Pharmacokinetic evaluation was conducted on all patients participating in the Endeavor US PK trial. Forty-three (43) patients received the Endeavor Zotarolimus-Eluting Coronary Stent System; six patients received overlapping stents.

Blood samples (5 mL) were collected at 30 days post-procedure. Selected pharmacokinetic parameters for the Endeavor US PK study analysis are provided in Table 7.

Table 7: Endeavor US PK Results

PK Parameter	Units	Group I (90 µg) N = 1†	Group II (168 µg) N = 1†	Group III[a] (180 µg) N = 24	Group IV[a] (240 µg) N = 6	Group V (270 µg) N = 2†	Group VI[a] (300 µg) N = 7	Group VII (360 µg) N = 1†	Group VIII (420 µg) N = 1†
C_{max}	(ng/mL)	0.847	2.176	1.513 ± 0.616	1.83 ± 0.210	1.584	2.658 ± 0.998	2.539	3.133
T_{max}	(h)	1.00	4.00	1.2 ± 0.6	1.4 ± 1.3	1.5	1.5 ± 1.3	2.00	1.3
$AUC_{0\text{-last}}$	(ng•h/mL)	46.51	71.73	57.02 ± 13.46	63.83 ± 15.27	125.18	90.77 ± 19.51[#]	95.21	87.45
$AUC_{0\text{-inf}}$	(ng•h/mL)	56.57	78.28	66.61 ± 14.86	72.84 ± 19.96	136.65	101.45 ± 23.48[#]	113.85	99.82
β	(1/h)	0.010	0.013	0.012 ± 0.003	0.012 ± 0.002	0.010	0.012 ± 0.003	0.010	0.012
$t_{½}$‡	(h)	71.5[§]	53.7[§]	59.7 ± 14.4	57.5 ± 7.6	68.3	59.5 ± 16.1[#]	66.67[§]	58.4[§]
$Vd_β/F$	(L)	164.1	166.3	254.7 ± 74.5	288.5 ± 53.6	261.6	291.6 ± 113.7[#]	304.2	354.6
CL/F	(L/h)	1.6	2.1	2.8 ± 0.7	3.5 ± 1.0	2.9	3.1 ± 0.8[#]	3.2	4.2

Vdβ/F Apparent volume of distribution
C_{max} Maximum blood concentration
T_{max} Time to Cmax
$AUC_{0\text{-inf}}$ AUC from time 0 to infinity ($AUC_{0\text{-inf}}$).
$t_{½}$ Harmonic mean half-life
$AUC_{0\text{-last}}$ Area under the blood concentration-time curve (AUC) from time 0 to time of last measurable concentration

a. Primary dose groups
‡ Harmonic mean ± pseudo-standard deviation
† No SD was reported when N ≤ 2
# N = 6
CL/F Mean apparent clearance
§ Mean only

The results in Table 7 show that pharmacokinetics of zotarolimus were linear in the primary dose-proportionality evaluation, consisting of dose groups with N > 2 (180, 240 and 300 µg), following the implantation of Endeavor stents as illustrated by dose proportional increases in C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$. Mean apparent clearance and harmonic mean half-life for the primary dose groups ranged from 2.8 to 3.5 L/h and 57.5

to 59.7 hours, respectively. The mean time to reach peak systemic concentration (T_{max}) ranged from 1.2 to 1.5 hours after stent implantation. Additionally, this study showed that zotarolimus is released gradually into the systemic circulation without any evidence of dose dumping.

6. Drug Interactions

The effect of potential drug interactions on the safety or efficacy of the Endeavor stent has not been investigated. While no specific clinical data are available, drugs, like sirolimus, that act through the same binding protein (FKBP12) may interfere with the efficacy of zotarolimus. Zotarolimus is metabolized by CYP3A4, a human cytochrome P450 enzyme. When administered concomitantly with 200 mg ketoconazole bid, a strong inhibitor of CYP3A4, zotarolimus produces less than a 2-fold increase in $AUC_{0\text{-}inf}$ with no effect on C_{max}. Therefore, consideration should be given to the potential for drug interactions when deciding to place an Endeavor stent in a patient who is taking drugs that are known substrates or inhibitors of the cytochrome P450 isoenzyme CYP3A4. Systemic exposure of zotarolimus should also be taken into consideration if the patient is treated concomitantly with systemic immunosuppressive therapy.

Formal drug interaction studies have not been conducted with the Endeavor stent.

B. Biocompatibility Studies

A series of GLP biocompatibility tests and USP Physicochemical tests were conducted to demonstrate that the components of the Endeavor Zotarolimus-Eluting Coronary Stent System (OTW, RX and MX^2) are non-toxic. Tests were conducted on ethylene oxide-sterilized Endeavor coated stents, stent delivery systems (finished product) and polymer-only coated stainless steel (SS) coupons. These test articles were processed in the same manner as the finished Endeavor product. The polymer-only coated coupons did not include drug substance but were manufactured to simulate the processing of Endeavor Zotarolimus-Eluting Coronary Stent System with equivalent surface treatment, cross-linking and sterilization processes utilized. In all of these test systems, the materials were non-reactive and met all acceptance criteria. The results of the biocompatibility studies indicated that the Endeavor Zotarolimus-Eluting Coronary Stent System was biologically safe and acceptable for clinical use.

All biocompatibility testing was conducted in accordance with Good Laboratory Practices Regulations (21 CFR § 58) and with consideration of the following guidances:

- Guidance for Industry and FDA Staff, Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems. Document issued on January 13, 2005.
- International Standard ISO 10993-1, Biological Evaluation of Medical Devices: Evaluation and Testing.

Table 8 provides a summary of the biocompatibility testing conducted in support of the Endeavor Zotarolimus-Eluting Coronary Stent System.

Table 8: Summary of Biocompatibility Testing

Test Name	Test Description	Test Article	Result
Cytotoxicity	ISO 10993-5: *In Vitro* Cytotoxicity (L929 MEM Elution)	• Endeavor stent and delivery systems • Endeavor stent	Pass (non-cytotoxic)
Pyrogenicity	ISO-10993-11: Systemic Toxicity (Material Mediated Rabbit, Injection)	• Endeavor stent and delivery systems	Pass (non-pyrogenic)
Sensitization	ISO-10993-10: Sensitization (Guinea pig Maximization)	• Endeavor stent and delivery systems • Endeavor stent	Pass (non-sensitizing)
Acute Intracutaneous Reactivity	ISO-10993-10: Irritation (Injection)	• Endeavor stent and delivery systems • Endeavor stent	Pass (non-irritant)
Acute Systemic Toxicity	ISO-10993-11: Systemic Toxicity (Acute)	• Endeavor stent and delivery systems • Endeavor stent	Pass (non-toxic)
Hemocompatability	ISO-10993-4: *In Vivo* Thromboresistance	• Endeavor stent and delivery systems	Pass (non-thrombogenic)
	ISO-10993-4: C3a Complement Activation (*In Vitro*)	• Endeavor stent and delivery systems	Pass (non-complement activating)
	ISO-10993-4: SC5b9 Complement Activation (*In Vitro*)	• Endeavor stent and delivery systems	Pass (non-complement activating)
	ISO-10993-4: Plasma Recalcification	• Endeavor stent and delivery systems	Pass (no significant change in coagulation time)
	ISO-10993-4: *In Vitro* Hemolysis Study	• Endeavor stent and delivery systems • Endeavor stent	Pass (non-hemolytic)
	ISO-10993-4: White Blood Cell Morphology	• Endeavor stent and delivery systems	Pass (no change in WBC morphologically)

Table 8: Summary of Biocompatibility Testing

Test Name	Test Description	Test Article	Result
Genotoxicity	ISO-10993-3: Bacterial Reverse Mutation (AMES)	• Endeavor stent	Pass (non-mutagenic)
	ISO-10993-3: *In Vitro* Chromosomal Aberration in Mammalian Cells	• Endeavor stent	Pass (non-clastogenic)
	ISO-10993-3: *In Vivo* Mouse Bone Marrow Micronucleus Test	• Endeavor stent	Pass (non-mutagenic)
Material Characterization (USP Physicochemical Testing)	USP Physicochemical Extracts <661> (Aqueous)	• Balloon Material • Polyethylene Sheath • PC Polymer-only Coated Coupons	Pass

In vivo animal testing conducted on the Endeavor Zotarolimus-Eluting Coronary Stent System evaluated the effects of multiple doses and device exposure in a porcine coronary or rabbit iliac artery model for up to 180 days, in lieu of ISO 10993 sub-chronic and muscle implantation testing. The *in vivo* results indicated that the Endeavor Zotarolimus-Eluting Coronary Stent System was biologically safe and acceptable for clinical use. The significant animal studies are summarized separately in Section VIII. F – Animal Studies.

Formal carcinogenicity and reproductive toxicity testing was not conducted on the Endeavor Zotarolimus-Eluting Coronary Stent System. An appropriate rationale has been provided to demonstrate why the carcinogenic potential of the Endeavor stent is minimal based on the types and quantities of materials present and the limited period of zotarolimus release. The genotoxicity and reproductive toxicity of zotarolimus have been investigated in bacterial and mammalian cells *in vitro* and in laboratory animals *in vivo*.

There is no evidence to suggest that any chemical interactions occur between the PC polymer and zotarolimus drug under established processing and storage conditions that would lead to the formation of covalent bonds or that would alter the structure of the drug in any way to form a new intermediate or molecular entity.

Long term biocompatibility of the drug/polymer coating on the stent in humans is unknown.

C. *In Vitro* Engineering Testing

In vitro engineering testing, in accordance with FDA's "Guidance for Industry and FDA Staff: Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems" (January 13, 2005), was conducted on the Endeavor stent mounted on the OTW, RX, and/or MX^2 delivery systems.

Some *in vitro* engineering tests were performed on the uncoated, bare metal version of the Endeavor stent since there was no change to the stent substrate. An appropriate rationale was provided where the testing of the bare metal stent provided a worst case or

representative condition for the attributes evaluated. The effect of the coating is assumed to be negligible when evaluated against measurement and manufacturing tolerances.

Additional tests were conducted to support the integrity of the coating on the Endeavor Zotarolimus-Eluting Coronary Stent System and are summarized separately in Section VIII. D – Coating Characterization Testing.

The *in vitro* engineering studies conducted are summarized in Table 9. "Pass" denotes that the test results met product specifications and/or the recommendations in the referenced guidance documents.

Table 9: Stent and Delivery Catheter Engineering Testing

Test	Description of Test	Conclusion
Stent Material Specification Conformance Testing		
Material Characterization	Chemical analysis was conducted on the Co-Ni-Cr-Mo alloy provided by the material supplier to confirm chemical analysis and inclusion/impurity content as provided by ASTM F562 "Standard Specification for Wrought Cobalt-35 Nickel-20 Chromium-10 Molybdenum Alloy for Surgical Implant Applications."	Pass
Surface Contamination	SEM analysis was conducted to detect evidence of surface contaminants or impurities. Results of SEM evaluation showed no evidence of contamination above the specified limits.	Pass
Mechanical Properties	Testing was conducted to characterize the following properties of the annealed Co-Ni-Cr-Mo alloy bars: 0.2% offset yield strength, ultimate tensile strength, percent elongation, and reduction of area. Bars were machined from barstock conforming to ASTM F562. The bars were tensile tested to failure while engineering stress and strain were continuously recorded. The results were in conformance with ASTM F562.	Pass
Stent Corrosion Resistance	Endeavor stents were tested according to ASTM F2129 "Standard Test Method for Conducting Cyclic Potentiodynamic Measurements to Determine the Corrosion Susceptibility of Small Implant Devices" to demonstrate that the finished stents exhibit corrosion and repassivation characteristics comparable to marketed Driver stents. Results were comparable to the control stents and met product specification requirements. Testing was also conducted to evaluate the relative susceptibility to pitting/crevice corrosion of the Endeavor stent utilizing the corrosion techniques outlined in ASTM F746 and using sample preparation techniques in accordance with ASTM F2129. Results were comparable to marketed Driver stents and met product specification requirements.	Pass
Fretting Corrosion	Overlapped bare metal Driver or Micro-Driver stents were evaluated post fatigue testing to determine the potential for fretting corrosion. The results met all acceptance criteria and indicated that the stents possess a high resistance to fretting corrosion.	Pass

Table 9: Stent and Delivery Catheter Engineering Testing

Test	Description of Test	Conclusion
Galvanic Corrosion	Testing was conducted on marketed Driver stents (MP35N) overlapped with marketed S7 (316L stainless steel) stents to determine the potential for galvanic corrosion. The results met all acceptance criteria and indicated a high resistance to galvanic corrosion.	Pass
Stent Dimensional and Functional Attributes		
Stent Dimensional Verification	Testing was conducted to measure and optically inspect the stent to document that stent dimensional and visual specifications do not deviate from product specifications. All product met specifications.	Pass
Percent Surface Area	This value is calculated using stent nominal dimensional values and is based on the ratio of stent area to the area of the vessel. Metal to artery percentage ratios were calculated for all of the stent diameters recommended in the product labeling, with the highest surface to artery ratio (18.6%) occurring when the stent is deployed to the nominal diameter (2.5 mm) for the seven crown stent design and (19.9%) occurring when the stent is deployed to the nominal diameter (3.0 mm) for the ten crown stent design.	N/A Characterization only
Foreshortening	The length of the stents were measured prior to and after expansion to the largest nominal diameter. All stents met product specifications.	Pass
Stent Recoil	Testing was conducted to quantify the amount of elastic recoil for the stent and correlate this parameter to the recommended sizing procedures. The stent delivery system was inflated to nominal pressure and the stent was removed allowing for recoil to occur. The inner diameter at each end of the stent was recorded. Recoil was calculated by subtracting the recoiled stent inner diameter from the pre-recoil inner diameter. All stents met the acceptance criteria after balloon inflation to nominal pressure.	Pass
Stent Integrity	Testing was conducted to determine if the plastic deformation experienced by the stent when expanded from the compressed profile to the final maximum deployed diameter can produce crack initiation for the stent. Samples were deployed to their largest possible diameters by inflating each delivery system to nominal plus 0.5 mm. Each stent was examined under magnification for potential cracks. All samples met the acceptance criteria with no visible cracks or notches.	Pass
Radial Stiffness and Radial Strength	Testing was conducted to determine stent resistance to radial load. The stents were deployed to nominal stent diameter and placed in a radial crush tester. All samples met the acceptance criteria.	Pass
Stent Expansion/ Coating Evaluation	Testing was conducted to provide a qualitative comparison of Endeavor coating in the pre-deployed, deployed to nominal and deployed to maximum diameter conditions using microscopy. A qualitative comparison of coating integrity was also performed pre- and post tracking through a tortuous anatomy using microscopy and SEM.	N/A Characterization only See * note at end of table.

Table 9: Stent and Delivery Catheter Engineering Testing

<table>
<tr><th>Test</th><th colspan="2">Description of Test</th><th>Conclusion</th></tr>
<tr><td>Coating Stress Analysis</td><td colspan="2">A stress analysis, using a finite element analysis (FEA), demonstrated that the addition of a coating to a Driver or Micro-Driver stent will not change the critical location of stresses during expansion and during in vivo loading. Additionally, the coating stress analysis showed that the critical stress location within the coating is in the same location found on a bare stent.</td><td>Pass</td></tr>
<tr><td>Fatigue Analysis (FEA)</td><td colspan="2">An in-depth analysis of the stent was conducted to ensure that the implant conditions to which the stent will be subjected would not result in failure due to fatigue. The FEA evaluated the structural integrity of the stent when subjected to the expected loading conditions generated in coronary arteries. The analysis took into account manufacturing, delivery, implantation and clinical loading over the implant life, and predicted that fatigue failures will not likely occur.</td><td>Pass</td></tr>
<tr><td>Accelerated Durability Testing</td><td colspan="2">This testing was conducted to determine the fatigue integrity of a stent under accelerated cycling designed to model in vivo conditions. Stents were deployed up to the largest intended diameter and tested through a simulated 10 year life. After the completion of the ten year simulated durability testing, the stents were visually inspected using microscopy for cracking or breaks. All units tested were free of any cracks or breaks. There were no stent failures noted after 420 million cycles (equivalent to 10 years in vivo). Additionally, Endeavor stents were analyzed using SEM post accelerated durability testing.</td><td>Pass

See * note at end of table.</td></tr>
<tr><td>Magnetic Resonance Imaging (MRI) Safety and Compatibility</td><td colspan="2">Non-clinical testing on single and overlapped stents has demonstrated the Endeavor stent is MR Conditional. It can be scanned safely under the following conditions:
<table><tr><th>Single Stenting (Stent Length 30 mm)</th><th>Overlapped Stenting (Total Length 55 mm)</th></tr><tr><td>Static magnetic field of 3-Tesla</td><td>Static magnetic field of 3-Tesla</td></tr><tr><td>Spatial gradient field of 525 Gauss/cm</td><td>Spatial gradient field of 720 Gauss/cm</td></tr><tr><td>Maximum whole-body-averaged specific absorption rate (SAR) of 2 W/kg for 20 minutes of scanning</td><td>Maximum whole-body-averaged specific absorption rate (SAR) of 3 W/kg for 15 minutes of scanning</td></tr><tr><td>In non-clinical testing, the Endeavor stent produced a temperature rise of less than 0.5°C at a maximum whole body averaged specific absorption rate (SAR) of 2 W/kg for 20 minutes of MR scanning in a 3-Tesla, Signa, General Electric Medical Systems (software version 9.0) MR scanner. The maximum whole body averaged SAR was displayed on MR scanner console.</td><td>In non-clinical testing, the Endeavor stent produced a temperature rise of less than 0.5°C at a maximum whole body averaged specific absorption rate (SAR) of 3 W/kg for 15 minutes of MR scanning in a 3-Tesla, Excite, General Electric Healthcare (software version G3.0-052B) MR scanner. The maximum whole body averaged SAR was displayed on MR scanner console.</td></tr></table></td><td>N/A</td></tr>
</table>

Table 9: Stent and Delivery Catheter Engineering Testing

Test	Description of Test		Conclusion
	The Endeavor stent should not move or migrate when exposed to MR scanning immediately post-implantation.		
	The image artifact extends approximately 9 mm from the device/lumen centerline when scanned in nonclinical testing using a 3-Tesla, Signa, General Electric Medical Systems (software version 9.0) MR system with a send-receive RF body coil.	The image artifact extends approximately 10 mm from the device/lumen centerline when scanned in nonclinical testing using a 3-Tesla, Excite, General Electric Healthcare (software version G3.0-052B) MR system with a send-receive RF body coil.	
Radiopacity	The radiopacity of the Endeavor stent system was evaluated at delivery, deployment and after implantation in an *in vivo* animal study and radiopacity characteristics were sufficiently comparable to marketed cobalt alloy stents.		Pass
Stent ID Uniformity	This test was conducted to demonstrate that the deployed internal diameter of the Endeavor stent system is consistent with labeling. Each stent was deployed to nominal pressure, and the stent inner diameter was measured at each end. The results indicated that the Endeavor stent system expands uniformly at all diameters and maintains this uniformity upon withdrawal of the balloon.		Pass
Delivery System Dimensional and Functional Attributes			
Delivery, Deployment, and Retraction	*In vitro* testing was conducted to evaluate delivery, deployment, and retraction of the Endeavor stent delivery system through a simulated tortuous path according to the instructions for use. All results indicated that the system performed as intended and no damage to the stent was noted.		N/A Characterization only
Balloon Maximum Pressure	This test was conducted to demonstrate that the Endeavor stent system (with mounted stent) will not experience balloon, shaft, proximal adaptation or proximal/distal seal loss of integrity at or below the pressure required to expand the stent to its labeled diameter. Stent delivery systems were initially pressurized to 90 psi. The cycle was then repeated, increasing inflation pressure by 15 psi each cycle until failure. The results demonstrate with 95% confidence that at least 99.9% of the delivery systems will not experience loss of integrity at or below the rated burst pressure.		Pass
Balloon Fatigue	Endeavor stent systems were required to complete 10 unconstrained pressurization cycles to rated burst pressure (RBP). The stent/balloon burst results show statistically that, with 95% confidence, 90% of the delivery systems will not experience balloon, shaft, or proximal/ distal seal loss of integrity at or below the maximum recommended RBP.		Pass
Stent Diameter vs. Balloon Pressure (Compliance)	Testing was performed to determine how the stent inner diameter varies with applied inflation pressures. The stent sizing results verify that the stent systems meet the labeled compliance curves.		N/A Characterization for product labeling

Table 9: Stent and Delivery Catheter Engineering Testing

Test	Description of Test	Conclusion
Catheter Bond Strength	Testing was performed to confirm the bond strength specifications for the Endeavor stent delivery system. All bonds were loaded into the tensile tester and pulled to failure. All samples met the acceptance criteria.	Pass
Stent/Catheter Crossing Profile	Endeavor stents and delivery systems were tested to verify the crossing profile per label claims. All samples met product specifications.	Pass
Balloon Inflation and Deflation Time	Endeavor delivery systems were tested for inflation/deflation times. All samples met the product specification.	Pass
Stent Securement	• Testing was conducted to assess the force required to displace a crimped Endeavor stent from the Endeavor delivery system by both forward and reverse motion. All stent systems met the stent securement specification. • Testing was performed to characterize the performance of the Endeavor stent system (undeployed) to cross a simulated lesion post tracking through a tortuous artery model. The Endeavor product performed as intended. • To further characterize the performance of the Endeavor stent system undeployed stents were tracked through a tortuous artery model and withdrawn through the recommended guide catheter. The Endeavor product performed as intended.	Pass
Balloon Deflatability	This test was performed to provide assurance that the deflated delivery system balloons will release from the expanded stent without interference. All samples met specification.	Pass
Catheter Body Maximum Pressure	Testing was conducted on the Endeavor stent delivery systems to determine the ability of the catheter shaft to withstand inflation to balloon rated burst pressure. All samples met the product specification.	Pass

* *Note*:
Microcracks were observed in the drug/polymer coating layer of all samples both pre- and post simulated use and pre- and post durability testing. The location of microcracks did not appear to change from the pre- to the post deployed state. Microcracks were not observed in the cross-linked polymer base layer (i.e. the coating layer that remains implanted post drug exhaustion) after durability testing. Areas of apparent coating loss were observed on the inner and outer stent diameters; however areas of coating loss were predominantly on the ID surface of the stent.

D. Coating Characterization Testing

The following methods were developed to characterize and set initial specifications for the Endeavor Zotarolimus-Eluting Coronary Stent System. The coating characterization testing conducted on the Endeavor Zotarolimus-Eluting Coronary Stent System includes those tests summarized in Table 10.

Table 10: Coating Characterization Testing

Test	Description of Test
Materials Analysis – Polymer	Polymer components were tested to ensure conformity to raw materials specifications and incoming inspection procedures.
Chemical Analysis – Polymer	Assays were conducted to determine residual monomer content, residual solvent levels and water content.
Chemical Analysis – Drug	Drug substance was tested to ensure conformity to incoming Certificate of Analysis.
Total Drug Content	Assay was conducted to quantitatively determine the total amount of drug substance, zotarolimus, on the Endeavor stent system.
Dose Density	Dose per mm was calculated.
Drug Content along Stent Length	Testing was conducted to characterize the uniformity of distribution of drug along the length of the Endeavor stent system.
Total Drug Related Substances	Assays were conducted to quantitatively determine the type and amount of impurities and degradation products on the Endeavor stent system.
Coating Thickness	Testing was conducted to describe the coating thickness along the length of the stent.
In Vitro Elution	Assay was developed to measure the *in vitro* release kinetics of zotarolimus from the Endeavor stent system.
Particulates	Particulate levels were determined for the Endeavor stent system post tracking and deployment. All samples met product specifications.

Medtronic Vascular provided a letter from the polymer manufacturer, Biocompatibles Ltd., authorizing access to a Master File (MAF) in support of this submission.

E. Chemistry Manufacturing and Controls (CMC) Testing

Where applicable, International Conference on Harmonization (ICH) Guidelines were followed for the testing routinely performed on Endeavor stents as part of CMC. This testing is summarized in Table 11. Information to support the stability of the Endeavor stent is summarized separately in Section VIII. G – Stability below.

Table 11: CMC Release Testing

Test	Description of Test
Material Analysis – Polymer	The polymer was tested to ensure conformity to specifications. The polymer met specifications prior to utilization in finished goods.
Drug Identity	Assay was conducted to verify the identity of the drug substance, zotarolimus, on the Endeavor Zotarolimus-Eluting Coronary Stent System. The product met specifications established for finished goods release.
Drug Content/Impurities	Assays were conducted to quantitatively verify the amount of drug and the type and amount of impurities on the Endeavor Zotarolimus-Eluting Coronary Stent System. The product met specifications established for finished goods release.
Drug Content Uniformity	Multiple stents were assayed to verify the uniformity of the drug content between the individual stents was within specifications established for finished good release.
Residual Solvents	Assay was conducted on the Endeavor stent system to verify that residual levels of solvents used in the manufacturing process were below acceptable limits established for finished goods release.
In Vitro Elution	The *in vitro* release profile for zotarolimus was measured on the Endeavor stent system. Specifications were based on the elution characteristics of stents evaluated in the clinical investigation. The product met specifications established for finished goods release.
Particulates	Particulate levels were monitored to verify that they remain below acceptable levels as established in the product specifications.

F. Animal Studies

Detailed arterial histopathology and histomorphometry are not obtainable through human clinical trials. Consequently, a series of animal studies were conducted to evaluate safety, proof of concept and overall product performance.

Medtronic Vascular conducted a series of animal studies evaluating various zotarolimus-eluting stent formulations (e.g., drug dosages), polymer-coated control stents and/or bare metal control stents. These studies were conducted in coronary arteries of pigs, or iliac arteries of rabbits. Data from these studies served as the basis for the dose selection for the Endeavor Zotarolimus-Eluting Coronary Stent System used in the Endeavor clinical studies and provided an assessment of the safety of the product over a range of timepoints.

The intravascular safety and biocompatibility of zotarolimus-eluting stents were evaluated in a series of animal studies in a porcine model of stent-mediated vascular injury. Non-GLP studies were conducted in order to provide additional background data for non-safety related areas. All study phases (feasibility, safety, pharmacokinetic and

acute) are represented by studies that were conducted in accordance with § 21CFR 58 (Good Laboratory Practices), except where noted. The results of these studies support the safety and biocompatibility of the Endeavor Zotarolimus-Eluting Coronary Stent System. Summaries of the major animal studies performed to support product safety are included in Table 12.

Table 12: Summary of Major Supportive Animal Studies

Study #	Stent Design	Stent Size (mm)	Type/ # of Animals	# of Stents	Follow-up Duration	Major Endpoints
FS102	Test Article: zotarolimus-eluting Endeavor stent system, multiple doses Control: BMS GLP: Yes	Diameter: • 3.0, 3.5, 4.0 mm Lengths: • 12, 18 mm	Domestic Swine Test and Control: 15 (LAD, LCX, RCA) One stent/vessel Animals received both test and control	Test: 32 Control: 20	7 days	• Angiographic patency • Histologic and histomorphometric evaluation of single and overlapping stents • Cell proliferation • Acute delivery
FS135	Test Article: zotarolimus-eluting Endeavor stent system, multiple doses Control: BMS and Polymer only coated stents GLP: Yes	Diameter: • 2.25, 2.5 mm Lengths: • 8 mm	Juvenile Yorkshire Swine Test and Control: 21 (LAD, LCX, RCA) One stent per vessel. Animals received both test and control.	Test: 24 Control: 20 Control (Polymer Coated Stents): 12	28 days	• Angiographic patency • Histologic and histomorphometric evaluation of exaggerated dose and Endeavor stent systems • Acute Delivery • Chronic vascular response at 28 days
FS99	Test Article: zotarolimus-eluting Endeavor stent system, multiple doses Control: BMS and Polymer only coated stents GLP: Yes	Diameter: • 2.5, 3.0, 3.5, 4.0 mm Lengths: • 12, 18 mm	Domestic Swine Test and Control : 51 (LAD, LCX, RCA) One stent per vessel. Animals received both test and control.	Test: 99 Control: 64 Control (Polymer Coated Stents): 13	28 days	• Angiographic patency • Histologic and histomorphometric evaluation of exaggerated dose, single and overlapping stents • Acute Delivery • Chronic vascular response at 28 days
FS100	Test Article: zotarolimus-eluting Endeavor stent system, multiple doses Control: BMS and Polymer only coated stents GLP: Yes	Diameter: • 2.5, 3.0, 3.5, 4.0 mm Lengths: • 12 mm	Yucatan Miniswine Test & Control: 31 (LAD, LCX, RCA) One stent per vessel. Animals received both test and control.	Test: 58 Control: 43 Control (Polymer Coated Stents): 9	90 days	• Angiographic patency • Histologic and histomorphometric evaluation of exaggerated dose, single and overlapping stents • Acute Delivery • Chronic vascular response at 90 days

Table 12: Summary of Major Supportive Animal Studies

Study #	Stent Design	Stent Size (mm)	Type/ # of Animals	# of Stents	Follow-up Duration	Major Endpoints
FS101	Test Article: zotarolimus-eluting Endeavor stent system, multiple doses Control: BMS and Polymer only coated stents GLP: Yes	Diameter: • 2.5, 3.0, 3.5, 4.0 mm Lengths: • 12 mm	Yucatan Miniswine Test & Control: 30 (LAD, LCX, RCA) One stent per vessel. Animals received both test and control.	Test: 55 Control: 40 Control (Polymer Coated Stents): 11	180 days	• Angiographic patency • Histologic and histomorphometric evaluation of exaggerated dose, single and overlapping stents • Acute delivery • Chronic vascular response at 180 days
FS114	Test Article: zotarolimus-eluting Endeavor stent system GLP: Yes	Diameter: • 3.0 mm Lengths: • 12 mm	Domestic Swine (LAD, LCX, RCA) One stent per vessel.	48	1, 2, 3, 5, 7, 10, 14 and 28 days	Evaluation of drug release rate, arterial drug levels & systemic drug levels over time.
FS161	Test Article: zotarolimus-eluting Endeavor stent system Control: BMS GLP: Yes	Diameter: • 3.0 mm Lengths: • 15 mm	Juvenile Yorkshire Swine Test and Control: 22 divided into 3 test and 1 control arms (LAD, LCX, RCA) One stent per vessel	Test: Endeavor RX: 6 Endeavor OTW: 5 Endeavor MX2: 6 Control: Driver OTW: 5	ACT level: 0, 3, 6, 9 and 11 days Angiography: 11 days	• Microscopic evaluation of the overall subacute tissue reaction of the vessel and the surrounding myocardium; examination of the thrombogenicity of the stent and delivery device at 11-days post-stenting • Acute delivery • Angiographic patency • Histologic and histomorphometric evaluation of test and controls • ACT levels at time of implant, 3, 6, and 9 days post-implant, at explant

BMS = bare metal stent – Driver for these studies.

The systemic toxicity of the intact Endeavor Zotarolimus-Eluting Coronary Stent System has been investigated in a number of studies that were intended principally to define the local tolerance and healing response to the implanted Endeavor Zotarolimus-Eluting Coronary Stent System (Studies FS97, FS99, FS100, FS101, FS102, FS110, FS124 and FS135). In these studies, body weight data, clinical laboratory measurements, necropsies, and histopathological examination of selected tissues from the animals implanted with stents demonstrated only infrequent adverse systemic effects and no systemic effects that could be attributed to stent implantation.

The efficacy of the zotarolimus incorporated into the coating of the Endeavor Zotarolimus-Eluting Coronary Stent System in inhibiting smooth muscle proliferation at the site of implantation has been examined in studies FS102 and FS107. In both studies, there were significantly fewer proliferating cells found in sections of stented tissue at 7 days post-implantation when zotarolimus was incorporated into the stent coating at 5 μg/mm or 10 μg/mm than when bare Driver stents were implanted.

The rate of elution of zotarolimus from the implanted Endeavor Zotarolimus-Eluting Coronary Stent System and the distribution of zotarolimus from the stent to surrounding arterial tissues, plasma, and distant organs has been measured using the rabbit iliac artery model (FS97) and the swine coronary artery model (FS114). These studies demonstrate that the drug rapidly elutes from the stent, with less than 50% of the drug remaining on the stent at 24 hours after implantation and less than 6% remaining at 7 days. Blood levels rapidly decline to undetectable levels by 7 days after implantation and peripheral tissues have highly limited exposures. Thus, while systemic exposure is limited, drug remains at the implantation site for at least 28 days.

The local tolerance and healing of coronary vessels after implantation of the Endeavor stent have been evaluated at various times (i.e., 7, 28, 90, and 180 days) after stent implantation into swine coronary arteries (Studies FS99, FS100, FS101, FS102, FS135) and rabbit iliac arteries (Study FS107). These studies demonstrate that initially the stent produced a slightly greater level of inflammation surrounding stents than the bare control Driver stents. This effect was observed early after implantation but did not persist. Also, a slight delay in endothelialization and fibrin removal between overlapped bare and overlapped drug-coated stents was observed. However, no differences in long-term healing attributable to the presence of the drug coating on the stents were observed. The slightly greater inflammation observed with the Endeavor stent did not result in greater levels of restenosis.

The effect of the stents on vascular healing after stent placement was also evaluated in both swine and rabbits. All of the stents exhibited complete endothelialization at both the 90 and 180 day timepoints.

G. Stability

Manufacturing site-specific stability studies were conducted to establish a shelf-life/expiration date for the Endeavor Zotarolimus-Eluting Coronary Stent System. Testing to establish package integrity and functional testing of the stent system were conducted on aged product. Testing evaluation included drug identity, assay, degradants, *in vitro* elution, particulates, sterility, drug content uniformity, residual solvents, and endotoxins. Appropriate engineering tests were also performed on aged product and compared to baseline to ensure that the Endeavor Zotarolimus-Eluting Coronary Stent System performed acceptably. The data generated support a shelf life of one year.

H. Sterilization

The Endeavor Zotarolimus-Eluting Coronary Stent System (OTW, RX, and MX^2 delivery systems) is sterilized using ethylene oxide sterilization, and has been validated per

AAMI/ISO 11135:1994 "Medical Devices – Validation and Routine Control of Ethylene Oxide Sterilization."

Results obtained from the sterilization studies show that the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6}.

The amount of bacterial endotoxins was verified to be within the specification limit for the Endeavor Zotarolimus-Eluting Coronary Stent System.

IX. Overview of Clinical Studies

The principal safety and efficacy information for the Endeavor stent is presented from the following clinical studies – the ENDEAVOR I trial, the ENDEAVOR II trial, the ENDEAVOR III trial and the ENDEAVOR IV trial. These studies have evaluated the performance of the Endeavor Stent in patients with symptomatic ischemic heart disease in single *de novo* lesions of native coronary arteries.

The ENDEAVOR I trial was the first-in-man study for the Endeavor stent. ENDEAVOR I was a non-randomized, prospective, multi-center, single-arm trial. The purpose of the trial was to assess the initial safety of the Endeavor stent. The primary endpoints in this trial were the rate of major adverse cardiac events (MACE) defined as composite of death, myocardial infarction (MI), emergent bypass surgery, or target lesion revascularization (TLR) at 30 days and in-segment late loss at 4 months as measured by quantitative coronary angiography (QCA). Post-procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 3 months.

The ENDEAVOR II trial was a prospective, multi-center, double-blind, two-arm randomized and controlled, superiority trial that compared the Endeavor stent to a control bare metal stent (the Driver stent). Eligibility was based on assessments of lesion reference vessel diameter and lesion length. The primary endpoint in this trial was the target vessel failure (TVF) rate, defined as the composite of cardiac death, MI, or clinically-driven target vessel revascularization (TVR) of the treated vessel at 9 months post-procedure. The powered secondary endpoint was in-segment late loss at 8 months measured by QCA. Post-procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 3 months.

The ENDEAVOR III trial was a prospective, multi-center, single-blind, two-arm randomized and controlled, non-inferiority trial that compared the Endeavor stent to a control DES (the Cypher stent). Eligibility was based on the assessments of a lesion reference vessel diameter and lesion length. The primary endpoint of this study was in-segment late loss at 8 months as measured by QCA and defined as the difference between post-procedure minimum lumen diameter (MLD) and the MLD at time of follow-up within the stented region and 5 mm proximal and distal to the edges of the stent. Post-procedure, patients received aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 3 months.

The ENDEAVOR IV trial was a prospective, multi-center, single-blind, two-arm randomized and controlled, non-inferiority trial that compared the Endeavor stent to a

control DES (the Taxus stent). Eligibility was based on the assessments of a lesion reference vessel diameter and lesion length. The primary clinical endpoint in this non-inferiority study was the TVF rate, defined as the composite of cardiac death, MI, or clinically-driven TVR of the treated vessel at 9 months post-procedure. The powered secondary endpoint was in-segment late loss at 8 months, measured by QCA. Post-procedure, patients received aspirin indefinitely and clopidogrel for a minimum of 6 months.

Table 13: Clinical Trial Comparisons

	ENDEAVOR I	ENDEAVOR II	ENDEAVOR III	ENDEAVOR IV
Study Type	Multi-center (n=8) Prospective Non-randomized	Multi-center (n=72) Prospective Randomized	Multi-center (n=29) Prospective Randomized	Multi-center (n=80) Prospective Randomized
Number of Patients	Total: 100 (Endeavor)	Total: 1197 (Endeavor: 598, Driver: 599)	Total: 436 (Endeavor: 323, Cypher:113)	Total: 1548 (Endeavor: 773, Taxus: 775)
Lesion Criteria	Single *de novo* lesion in native coronary artery ≤ 15 mm in length and ≥ 3.0 mm to ≤ 3.5 mm in diameter	Single *de novo* lesion in native coronary artery ≥ 14 mm and ≤ 27 mm in length and ≥ 2.25 mm to ≤ 3.5 mm in diameter	Single *de novo* lesion in native coronary artery ≥ 14 mm and ≤ 27 mm in length and ≥ 2.5 mm to ≤ 3.5 mm in diameter	Single *de novo* lesion in native coronary artery ≤ 27 mm in length and ≥ 2.5 mm to ≤ 3.5 mm in diameter
Product Used	Endeavor Stent on the Rapid Exchange Stent Delivery System	Endeavor Stent on the Rapid Exchange Stent Delivery System	Endeavor Stent on the Over-The -Wire Stent Delivery System	Endeavor Stent on the Over-The -Wire Stent Delivery System
Antiplatelet Therapy	Aspirin indefinitely and clopidogrel or ticlopidine for ≥ 3 months.	Aspirin indefinitely and clopidogrel or ticlopidine for ≥ 3 months.	Aspirin indefinitely and clopidogrel or ticlopidine for ≥ 3 months.	Aspirin indefinitely and clopidogrel or ticlopidine for ≥ 6 months
Follow up	30 days: clinical 4 & 12 months: clinical and angiographic/IVUS 9 month: clinical 1-5 years: telephone	30 days: clinical 8 months: clinical and angiographic/IVUS 9 month: clinical 6 month, 1-5 years: telephone	30 days: clinical 8 months: clinical and angiographic/IVUS 9 month: clinical 6 month, 1-5 years: telephone	30 days: clinical 8 months: clinical and angiographic/IVUS 9 month: clinical 6 month, 1-5 years: telephone
Status	48 month follow-up complete. Yearly follow up to 5 years is ongoing.	36 month follow-up is complete. Yearly follow up to 5 years is ongoing.	24 month follow-up is complete. Yearly follow up to 5 years is ongoing.	9 month follow-up is complete. Yearly follow up to 5 years is ongoing.

Two additional single-arm non-randomized trials were reviewed by FDA: the ENDEAVOR II Continued Access study and the ENDEAVOR PK study. The objective of the ENDEAVOR II Continued Access registry was to collect additional acute safety information and performance data of the Endeavor stent. The primary endpoint was MACE at 30 days. The objective of the ENDEAVOR PK study was to assess the pharmacokinetic profile of the Endeavor stent (see Section VIII. A – 5 *In Vivo* Pharmacokinetics). These trials provide additional data on Endeavor stent use. Results of these studies have been pooled with the patients treated with Endeavor stents in Endeavor I, II, III, and IV studies described above in a post-hoc patient-level analysis to provide an enhanced estimate of the incidence of low-frequency events and outcomes in specific patient subgroups (see Section XI. F Overall Results of the ENDEAVOR Clinical Program (ENDEAVOR I, II, II-CA, III, IV and USPK)).

The Endeavor MX^2 delivery system was not used in the Endeavor clinical investigations (ENDEAVOR I to IV). The Endeavor MX^2 utilizes a modified shaft to facilitate the multi-exchange feature of the delivery system.

The distal section of the Endeavor MX^2 Zotarolimus-Eluting Coronary Stent System, including the stent, balloon, drug coating and stent interfaces are identical to that of the Endeavor RX and OTW delivery systems which were studied clinically. Appropriate pre-clinical testing was provided to support the Endeavor MX^2 delivery system. Acute and long term safety and performance data is provided in the PMA application (ENDEAVOR I to IV clinical investigations, over 2000 patients) to support the clinical safety and efficacy of the Endeavor stent mounted on the Endeavor delivery systems.

X. Adverse Events

A. Observed Adverse Events

Observed adverse event experience with the Endeavor stent comes from four clinical studies: the ENDEAVOR IV, the ENDEAVOR III, the ENDEAVOR II, and the ENDEAVOR I trials.

The ENDEAVOR IV, III, II, and I trials have evaluated the performance of the Endeavor stent in patients with symptomatic ischemic heart disease in single *de novo* lesions of native coronary arteries. Principal adverse events are shown in Table 14.

Table 14: ENDEAVOR IV, III, II and I - Principal Adverse Events from Post-procedure to Latest Follow-up

	ENDEAVOR IV		ENDEAVOR III		ENDEAVOR II		ENDEAVOR I
	Endeavor N = 773	Taxus N = 775	Endeavor N = 323	Cypher N = 113	Endeavor N = 598	Driver N = 599	Endeavor N = 100
In-Hospital							
MACE	0.9% (7/773)	2.6% (20/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.9% (17/596)	0% (0/100)
Total Death	0% (0/773)	0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.2% (1/597)	0.0% (0/596)	0.0% (0/100)
Cardiac Death	0.0% (0/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.2% (1/597)	0.0% (0/596)	0.0% (0/100)
Non-Cardiac Death	0.0% (0/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
MI	0.8% (6/773)	2.1% (16/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.7% (16/596)	0.0% (0/100)
Q wave MI	0.3% (2/773)	0.1% (1/775)	0.0% (0/323)	0.0% (0/113)	0.2% (1/597)	0.3% (2/596)	0.0% (0/100)
Non-Q wave MI	0.5% (4/773)	1.9% (15/775)	0.6% (2/323)	3.5% (4/113)	2.3% (14/597)	2.3% (14/596)	0.0% (0/100)
TVR	0.4% (3/773)	0.6% (5/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)
TLR	0.4% (3/773)	0.5% (4/775)	0.0% (0/323)	0.0% (0/113)	0.5% (3/597)	0.3% (2/596)	0.0% (0/100)
Non-TLR	0.0% (0/773)	0.3% (2/775)	0.0% (0/323)	0.0% (0/113)	0.0% (0/597)	0.0% (0/596)	0.0% (0/100)
Cardiac death or MI	0.8% (6/773)	2.1% (16/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.7% (16/596)	0.0% (0/100)
TVF	0.9% (7/773)	2.6% (20/775)	0.6% (2/323)	3.5% (4/113)	2.5% (15/597)	2.9% (17/596)	0.0% (0/100)
Stent thrombosis (protocol)	0.3% (2/773)	0.0% (0/775)	0.0% (0/323)	0.0% (0/113)	0.3% (2/597)	0.3% (2/596)	0.0% (0/100)
Data at 9 Months							
MACE	5.7% (42/740)	5.7% (42/734)	7.5% (24/321)	7.1% (8/113)	7.3% (43/592)	14.4% (85/591)	2.0% (2/100)
Total Death	0.7% (5/740)	0.8% (6/734)	0.6% (2/321)	0.0% (0/113)	1.2% (7/592)	0.5% (3/591)	0.0% (0/100)
Cardiac Death	0.4% (3/740)	0.3% (2/734)	0.0% (0/321)	0.0% (0/113)	0.8% (5/592)	0.5% (3/591)	0.0% (0/100)
Non-Cardiac Death	0.3% (2/740)	0.5% (4/734)	0.6% (2/321)	0.0% (0/113)	0.3% (2/592)	0.0% (0/591)	0.0% (0/100)
MI	1.5% (11/740)	2.5% (18/734)	0.6% (2/321)	3.5% (4/113)	2.7% (16/592)	3.9% (23/591)	1.0% (1/100)
Q wave MI	0.3% (2/740)	0.1% (1/734)	0.0% (0/321)	0.0% (0/113)	0.3% (2/592)	0.8% (5/591)	0.0% (0/100)
Non-Q wave MI	1.2% (9/740)	2.3% (17/734)	0.6% (2/321)	3.5% (4/113)	2.4% (14/592)	3.0% (18/591)	1.0% (1/100)
TVR	5.5% (41/740)	5.0% (37/734)	11.2% (36/321)	8.0% (9/113)	5.6% (33/592)	12.5% (74/591)	2.0% (2/100)
TLR	4.2% (31/740)	2.7% (20/734)	6.2% (20/321)	3.5% (4/113)	4.6% (27/592)	11.8% (70/591)	2.0% (2/100)
Non-TLR	2.0% (15/740)	2.9% (21/734)	5.9% (19/321)	5.3% (6/113)	1.5% (9/592)	2.2% (13/591)	0.0% (0/100)
Cardiac death or MI	1.9% (14/740)	2.7% (20/734)	0.6% (2/321)	3.5% (4/113)	3.4% (20/592)	4.4% (26/591)	1.0% (1/100)
TVF	6.8% (50/740)	7.4% (54/734)	11.8% (38/321)	11.5% (13/113)	7.9% (47/592)	15.1% (89/591)	2.0% (2/100)
Stent thrombosis (protocol)	0.8% (6/740)	0.1% (1/734)	0.0% (0/321)	0.0% (0/113)	0.5% (3/592)	1.2% (7/591)	1.0% (1/100)
1-year MACE	NA	NA	7.8% (25/320)	8.0% (9/112)	8.8% (52/590)	15.6% (92/589)	2.0% (2/99)
2-year MACE	NA	NA	9.3% (29/313)	11.6% (13/112)	9.9% (58/587)	18.1% (106/586)	3.0% (3/99)
3-year MACE	NA	NA	NA	NA	12.0% (69/577)	20.7% (120/579)	6.1% (6/98)

Table 14: ENDEAVOR IV, III, II and I - Principal Adverse Events from Post-procedure to Latest Follow-up

	ENDEAVOR IV		ENDEAVOR III		ENDEAVOR II		ENDEAVOR I
	Endeavor N = 773	Taxus N = 775	Endeavor N = 323	Cypher N = 113	Endeavor N = 598	Driver N = 599	Endeavor N = 100
4-year MACE	NA	NA	NA	NA	NA	NA	7.2% (7/97)
Latest Data Available	**9 Months**		**24 Months**		**36 Months**		**48 Months**
MACE	5.7% (42/740)	5.7% (42/734)	9.3% (29/313)	11.6% (13/112)	12.0% (69/577)	20.7% (120/579)	7.2% (7/97)
Total Death	0.7% (5/740)	0.8% (6/734)	1.6% (5/313)	4.5% (5/112)	3.3% (19/577)	4.5% (26/579)	4.1% (4/97)
Cardiac Death	0.4% (3/740)	0.3% (2/734)	0.0% (0/313)	0.9% (1/112)	1.6% (9/577)	2.4% (14/579)	0.0% (0/97)
Non-Cardiac Death	0.3% (2/740)	0.5% (4/734)	1.6% (5/313)	3.6% (4/112)	1.7% (10/577)	2.1% (12/579)	4.1% (4/97)
MI	1.5% (11/740)	2.5% (18/734)	0.6% (2/313)	3.6% (4/112)	3.3% (19/577)	4.3% (25/579)	1.0% (1/97)
Q wave MI	0.3% (2/740)	0.1% (1/734)	0.0% (0/313)	0.0% (0/112)	0.3% (2/577)	1.0% (6/579)	0.0% (0/97)
Non-Q wave MI	1.2% (9/740)	2.3% (17/734)	0.6% (2/313)	3.6% (4/112)	2.9% (17/577)	3.3% (19/579)	1.0% (1/97)
TVR	5.5% (41/740)	5.0% (37/734)	13.7% (43/313)	9.8% (11/112)	9.5% (55/577)	17.6% (102/579)	5.2% (5/97)
TLR	4.2% (31/740)	2.7% (20/734)	7.0% (22/313)	4.5% (5/112)	7.3% (42/577)	14.7% (85/579)	3.1% (3/97)
Non-TLR	2.0% (15/740)	2.9% (21/734)	8.3% (26/313)	6.3% (7/112)	2.9% (17/577)	4.8% (28/579)	2.1% (2/97)
Cardiac death or MI	1.9% (14/740)	2.7% (20/734)	0.6% (2/313)	3.6% (4/112)	4.5% (26/577)	6.7% (39/579)	0.0% (0/0)
TVF	6.8% (50/740)	7.4% (54/734)	14.4% (45/313)	13.4% (15/112)	12.8% (74/577)	21.4% (124/579)	5.2% (5/97)
Stent thrombosis (protocol)	0.8% (6/740)	0.1% (1/734)	0.0% (0/313)	0.0% (0/112)	0.5% (3/577)	1.2% (7/579)	1.0% (1/97)

NA= Not Applicable; variable and/or time point not calculated
N = The maximum number of eligible patients.
The numbers are % (Count/Sample Size).
Major adverse cardiac events (MACE) is defined as composite of death, MI (Q wave and non-Q wave), emergent bypass surgery, or target lesion revascularization (repeat PTCA or CABG).
Q wave MI (QMI) defined when any occurrence of chest pain or other acute symptoms consistent with myocardial ischemia and new pathological Q waves in two or more contiguous ECG leads as determined by an ECG core laboratory or independent review of the CEC, in the absence of timely cardiac enzyme data, or new pathologic Q waves in two or more contiguous ECG leads as determined by an ECG core laboratory or independent review of the CEC and elevation of cardiac enzymes. In the absence of ECG data the CEC may adjudicate Q wave MI based on the clinical scenario and appropriate cardiac enzyme data.
Non-Q Wave MI (NQMI) is defined as elevated CK ≥ 2X the upper laboratory normal with the presence of elevated CK-MB (any amount above the institution's upper limit of normal) in the absence of new pathological Q waves.
Stent Thrombosis: See section XI.F1 for the per protocol stent thrombosis definition.
Target vessel failure (TVF) is defined as a composite of cardiac death, myocardial infarction, or clinically-driven target vessel revascularization.
Target lesion revascularization (TLR) is defined as any clinically-driven repeat intervention of the target lesion by PCI or CABG of the target vessel.
Target vessel revascularization (TVR) is defined as any clinically driven repeat intervention of the target vessel by PCI or CABG.

B. Potential Adverse Events

Adverse events associated with using this product are those associated with percutaneous coronary diagnostic (including angiography and IVUS) and treatment procedures. These risks may include, but are not limited to, the following:

- Abrupt vessel closure
- Access site pain, hematoma or hemorrhage
- Allergic reaction (to contrast, antiplatelet therapy, stent material, or drug and polymer coating)
- Aneurysm, pseudoaneurysm, or arteriovenous fistula (AVF)
- Arrhythmias
- Balloon rupture
- Cardiac tamponade
- Coronary artery occlusion, perforation, rupture, or dissection
- Coronary artery spasm
- Death
- Embolism (air, tissue, device, or thrombus)
- Emergency surgery: peripheral vascular or coronary bypass
- Failure to deliver the stent
- Hemorrhage requiring transfusion
- Hypotension/hypertension
- Incomplete stent apposition
- Infection or fever
- Late or very late thrombosis
- Myocardial infarction (MI)
- Myocardial ischemia
- Peripheral ischemia/peripheral nerve injury
- Renal failure
- Restenosis of the stented artery
- Rupture of native or bypass graft
- Shock/pulmonary edema
- Stent deformation, collapse, or fracture
- Stent migration
- Stent misplacement
- Stroke/transient ischemic attack
- Thrombosis (acute and subacute)
- Unstable angina
- Ventricular fibrillation

Patients' exposure to zotarolimus is directly related to the total amount of stent length implanted.

The adverse events that have been associated with the intravenous injection of zotarolimus in humans include:

- Anemia
- Application site reaction
- Diarrhea
- Dry skin
- Headache
- Hematuria
- Infection
- Injection site reaction
- Pain (abdominal, arthralgia, injection site)
- Rash

In addition, thirty-day adverse event information was provided on over 2000 patients treated with the Endeavor Zotarolimus-Eluting Coronary Stent System to support the safety profile of zotarolimus. There may be other potential adverse events that are unforeseen at this time.

XI. Summary of Clinical Studies

A. Results of the ENDEAVOR IV Trial

Primary Objective: To demonstrate the non-inferiority in safety and efficacy of the Endeavor Zotarolimus-Eluting Coronary Stent System when compared to the Taxus Express 2 Paclitaxel-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries with a reference vessel diameter of 2.5 mm to 3.5 mm and lesion length of $\leq$ 27 mm.

Design: This was a prospective, multi-center, single-blind, two-arm, randomized and controlled non-inferiority trial that compared the Endeavor stent to a control DES (the Taxus stent). A total of 1548 patients were enrolled at 80 study sites in the United States who presented with symptomatic ischemic heart disease attributable to stenotic lesions of the native coronary arteries that were amenable to treatment by stenting. Patients were stratified by diabetic status and subsequently randomized to receive either the Endeavor or Taxus stent in a 1:1 ratio. Multiple stents were allowed for bailout only.

Follow-up was performed at 30 days, 6, 8, and 9 months, and will be performed at 12 months, and annually thereafter out to 5 years. The first 328 consecutively enrolled patients (across all sites) were scheduled to have angiographic and IVUS evaluations at 8 months. Following the index procedure, patients were treated with aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 6 months.

Demographics: The mean age was 63.5 years for patients in the Endeavor arm and 63.6 years for patients in the Taxus arm. The Endeavor arm had 66.9% (517/773) males, and the Taxus arm had 68.5% (531/775) males. In the Endeavor arm, 28.2% (218/773) of patients had prior percutaneous coronary revascularization, compared to 29.5% (229/775) of patients in the Taxus arm. In the Endeavor arm, 31.2% (241/773) of patients had a history of diabetes mellitus, compared to 30.5% (236/775) of patients in the Taxus arm. Patients were well-matched for baseline demographics with no statistically significant differences between treatment arms.

Results: The primary and secondary endpoints, protocol-defined stent thrombosis, and the latest available follow-up results are presented below (Table 15, Table 16, Table 17 and Figure 3).

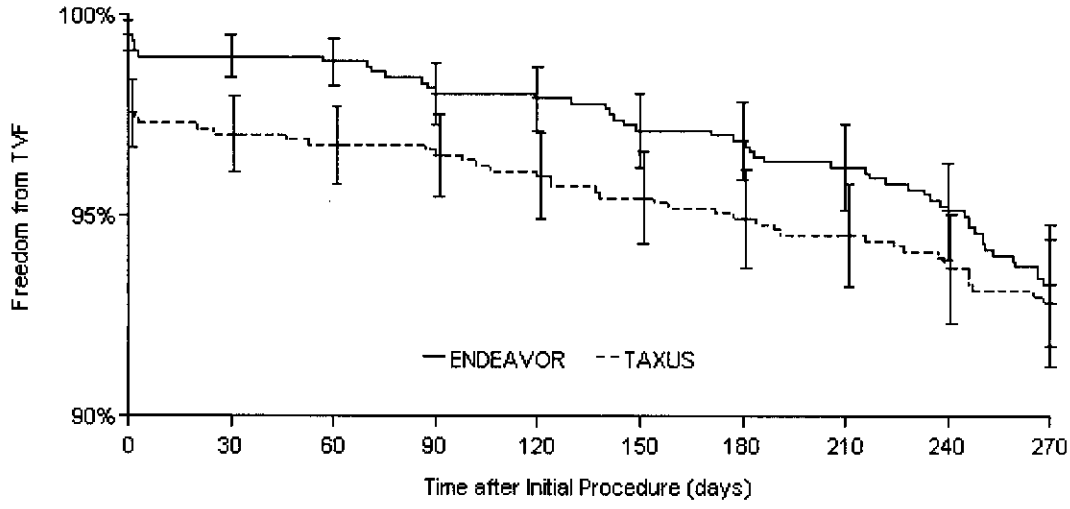
The primary endpoint of TVF at 9 months was met with 6.8% (50/740) for the Endeavor arm and 7.4% (54/734) for the Taxus arm ($p < 0.001$ for non-inferiority).

The pre-specified secondary endpoint of in-segment late loss at 8 months was not met with measurements of 0.36 ± 0.47 mm (143) for the Endeavor arm and 0.23 ± 0.45 mm (135) for the Taxus arm ($p = 0.0890$ for non-inferiority)

Table 15: ENDEAVOR IV Clinical Results

	Outcomes at 9 Months		
	Endeavor (N = 773)	**Taxus (N = 775)**	**P-Value**
PRIMARY ENDPOINT			
TVF§	6.8% (50/740)	7.4% (54/734)	< 0.001*
§ 9-month primary endpoint. * Test for non-inferiority.			
EFFICACY			
TVR	5.5% (41/740)	5.0% (37/734)	0.727**
TLR	4.2% (31/740)	2.7% (20/734)	0.154**
TLR, PCI	3.8% (28/740)	1.9% (14/734)	0.041**
TLR, CABG	0.5% (4/740)	0.8% (6/734)	0.546**
Non-TLR	2.0% (15/740)	2.9% (21/734)	0.316**
Non-TLR, PCI	1.8% (13/740)	2.5% (18/734)	0.370**
Non-TLR, CABG	0.4% (3/740)	0.4% (3/734)	1.000**
SAFETY			
Total Death	0.7% (5/740)	0.8% (6/734)	0.773**
Cardiac Death	0.4% (3/740)	0.3% (2/734)	1.000**
Non-Cardiac Death	0.3% (2/740)	0.5% (4/734)	0.450**
Cardiac Death or MI	1.9% (14/740)	2.7% (20/734)	0.303**
MI	1.5% (11/740)	2.5% (18/734)	0.194**
Q wave MI	0.3% (2/740)	0.1% (1/734)	1.000**
Non-Q wave MI	1.2% (9/740)	2.3% (17/734)	0.117**
Stent Thrombosis (protocol)	0.8% (6/740)	0.1% (1/734)	0.124**

** P-values for outcome differences are not adjusted for multiple comparisons.
Notes:
Fisher's Exact test was used for P-values.
This trial was not adequately powered to compare the rate of low frequency events, nor was it sized to determine the rate of low frequency events with a pre-specified precision.
Numbers are % (Count/Sample Size).
To be included in the event rate calculation for a given interval, a patient either had to have an event before the time of interest or they had to be event-free before the lower window of the follow-up.



TVF	Event Free	Event rate	P-Value*
ENDEAVOR	93.3%	6.7%	0.626
TAXUS	92.8%	7.2%	

* Log-rank P-value. P-value is not adjusted for multiple comparisons.

Figure 3: Survival Free from Target Vessel Failure (at 270 days)

Table 16: Endeavor IV 8-Month Angiographic and IVUS Results

	Endeavor (N = 773)	Taxus (N = 775)	P-Value
SECONDARY ENDPOINT			
Late Loss, In-segment (mm)¥	0.36 ± 0.47 (143)	0.23 ± 0.45 (135)	0.089*
¥ Powered secondary endpoint. * Test for non-inferiority.			
OTHER ANGIOGRAPHIC RESULTS			
MLD (mm), In-stent			
Post-Procedure	2.62 ± 0.43 (763)	2.61 ± 0.44 (763)	0.703**
8-Month	1.95 ± 0.61 (143)	2.25 ± 0.61 (135)	< 0.001**
MLD (mm), In-segment			
Post-Procedure	2.22 ± 0.47 (770)	2.19 ± 0.50 (772)	0.196**
8-Month	1.80 ± 0.55 (144)	1.98 ± 0.56 (135)	0.008**
% DS, In-stent			
Post-Procedure	5.50 ± 9.61 (763)	5.01 ± 10.49 (763)	0.348**
8-Month	26.41 ± 19.74 (143)	16.09 ± 17.99 (135)	< 0.001**
% DS, In-segment			
Post-Procedure	20.47 ± 9.54 (770)	20.97 ± 11.12 (772)	0.344**
8-Month	32.28 ± 17.02 (144)	26.61 ± 15.52 (135)	0.004**
Late Loss, In-stent (mm)	0.67 ± 0.49 (142)	0.42 ± 0.50 (135)	< 0.001**
Binary Restenosis			
In-stent Restenosis	13.3% (19/143)	6.7% (9/135)	0.075**
In-segment Restenosis	15.3% (22/144)	10.4% (14/135)	0.284**
IVUS RESULTS			
Neointimal Volume (mm^3)	24.14 ±19.38 (74)	14.88 ±16.62 (77)	0.002**
% Volume Obstruction	15.72 ±10.40 (74)	9.88 ±9.24 (77)	< 0.001**
Incomplete Apposition			
Post-procedure	12.5% (17/136)	11.8% (15/127)	1.000**
8-Month	10.0% (12/120)	14.7% (17/116)	0.324**
Resolved	3.8% (4/106)	2.1% (2/95)	0.686**
Persistent	8.5% (9/106)	10.5% (10/95)	0.638**
Late Acquired	0.9% (1/106)	3.2% (3/95)	0.346**

** P-values for outcome differences are not adjusted for multiple comparisons.
Note:
Fisher's Exact test or Student's t-test was used for P-values.

Table 17: ENDEAVOR IV Protocol-Defined Stent Thrombosis* Through 9 Months

	Endeavor (N = 773)	Taxus (N = 775)	P-Value
Cumulative ST through 9 Months	0.8% (6/740)	0.1% (1/734)	0.124**
Acute ST (≤ 24 hrs)	0.0% (0/770)	0.0% (0/771)	--
Subacute ST (> 24 hrs and ≤ 30days)	0.4% (3/770)	0.1% (1/771)	0.374**
Late ST (> 30 days and ≤ 9 months)	0.4% (3/740)	0.0% (0/734)	0.250**

* See section XI.F1 for the per protocol stent thrombosis definition.
** P-values for outcome differences are not adjusted for multiple comparisons.
Notes:
Fisher's Exact test was used for P-values.
This trial was not adequately powered to compare the rate of low frequency events, nor was it sized to determine the rate of low frequency events with a pre-specified precision.
To be included in the event rate calculation for a given interval, a patient either had to have an event before the time of interest or they had to be event-free before the lower window of the follow-up.
Numbers are % (Count/Sample Size).

B. Results of the ENDEAVOR III Clinical Trial

Primary Objective: To demonstrate non-inferiority in in-segment late loss at 8 months between the Endeavor Zotarolimus-Eluting Coronary Stent System and the Cypher Sirolimus-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries with a reference vessel diameter of 2.5 mm to 3.5 mm and lesion lengths of ≥ 14 mm and ≤ 27 mm.

Design: This was a prospective, multi-center, single-blind, two-arm, randomized and controlled non-inferiority trial that compared the Endeavor stent to a control DES (the Cypher stent). A total of 436 patients were enrolled at 29 study sites in the United States who presented with symptomatic ischemic heart disease attributable to stenotic lesions of native coronary arteries that were amenable to treatment by stenting. Patients were randomized to receive either an Endeavor or a Cypher stent in a 3:1 ratio. Multiple stents were allowed for bailout only.

Follow-up was performed at 30 days, 6, 8, 9, 12 months, and at 2 years, and will be performed annually thereafter out to 5 years. All patients were scheduled to have angiographic and IVUS evaluations at 8 months. Following the index procedure, patients were treated with aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 3 months.

Demographics: The mean age was 61.4 years for patients in the Endeavor arm and 61.7 years for patients in the Cypher arm. The Endeavor arm had 65.3% (211/323) males and the Cypher arm had 81.4% (92/113) males. In the Endeavor arm, 22.6% (73/323) of patients had prior percutaneous coronary revascularization compared to 16.8% (19/113) of patients in the Cypher arm. In the Endeavor arm, 29.7% (96/323) of patients had a history of diabetes mellitus compared to 28.3% (32/113) of patients in the Cypher arm. Patients were well matched for baseline demographics, with gender being the only significant difference between treatment arms.

Results: The primary and secondary endpoints, protocol-defined stent thrombosis, and the latest available follow-up results are presented below (Table 18, Table 19, and Table 20).

The primary endpoint of in-segment late loss at 8 months was not met with measurements of 0.36 ± 0.46 mm (277) for the Endeavor arm and 0.13 ± 0.33 mm (94) for the Cypher arm ($p < 0.791$ for non-inferiority). Differences noted in baseline demographics (gender) did not result in a significant impact on study outcomes.

Table 18: Endeavor III 8-Month Angiographic and IVUS Results

	Endeavor (N = 323)	Cypher (N = 113)	P-Value
PRIMARY ENDPOINT			
Late Loss, In-segment (mm) §	0.36 ± 0.46 (277)	0.13 ± 0.33 (94)	0.791*
§ 8-month primary endpoint. * Test for non-inferiority.			
OTHER ANGIOGRAPHIC RESULTS			
MLD (mm), In-stent			
Post-Procedure	2.67 ± 0.42 (323)	2.67 ± 0.40 (112)	0.993**
8-Month	2.06 ± 0.57 (277)	2.52 ± 0.56 (94)	< 0.001**
MLD (mm), In-segment			
Post-Procedure	2.27 ± 0.45 (323)	2.28 ± 0.47 (113)	0.836**
8-Month	1.91 ± 0.53 (277)	2.16 ± 0.50 (94)	< 0.001**
% DS, In-stent			
Post-Procedure	4.33 ± 9.77 (323)	5.92 ± 9.07 (112)	0.132**
8-Month	24.90 ± 17.45 (277)	11.01 ± 15.91 (94)	< 0.001**
% DS, In-segment			
Post-Procedure	19.38 ± 9.25 (323)	20.17 ± 11.74 (113)	0.522**
8-Month	30.42 ± 15.57 (277)	23.86 ± 13.87 (94)	< 0.001**
Late Loss, In-stent (mm)	0.62 ± 0.49 (277)	0.15 ± 0.34 (94)	< 0.001**
Binary Restenosis			
In-stent Restenosis	9.7% (27/277)	2.1% (2/94)	0.014**
In-segment Restenosis	12.3% (34/277)	4.3% (4/94)	0.029**
IVUS RESULTS			
Neointimal Volume (mm^3)	24.09 ± 21.16 (209)	3.74 ± 5.20 (67)	< 0.001**
% Volume Obstruction	15.94 ± 10.94 (187)	2.66 ± 3.11 (61)	< 0.001**
Incomplete Apposition			
Post-procedure	12.4% (31/251)	17.7% (17/96)	0.224**
8-Month	7.5% (17/226)	17.1% (13/76)	0.025**
Resolved	5.8% (11/189)	7.4% (5/68)	0.770**
Persistent	7.9% (15/189)	11.8% (8/68)	0.332**
Late Acquired	0.5% (1/189)	5.9% (4/68)	0.018**

** P-values for outcome differences are not adjusted for multiple comparisons.
Note:
Fisher's Exact test or Student's t-test was used for P-values.

Table 19: ENDEAVOR III Clinical Results

	Outcomes at 9 Months			Outcomes at 24 Months (latest available follow-up)		
	Endeavor (N = 323)	Cypher (N = 113)	P-Value	Endeavor (N = 323)	Cypher (N = 113)	P-Value
EFFICACY						
TVF	11.8% (38/321)	11.5% (13/113)	1.000**	14.4% (45/313)	13.4% (15/112)	0.875**
TVR	11.2% (36/321)	8.0% (9/113)	0.375**	13.7% (43/313)	9.8% (11/112)	0.325**
TLR	6.2% (20/321)	3.5% (4/113)	0.346**	7.0% (22/313)	4.5% (5/112)	0.498**
TLR, PCI	5.3% (17/321)	3.5% (4/113)	0.612**	5.8% (18/313)	4.5% (5/112)	0.808**
TLR, CABG	0.9% (3/321)	0.0% (0/113)	0.571**	1.3% (4/313)	0.0% (0/112)	0.577**
Non-TLR	5.9% (19/321)	5.3% (6/113)	1.000**	8.3% (26/313)	6.3% (7/112)	0.545**
Non-TLR, PCI	5.6% (18/321)	5.3% (6/113)	1.000**	7.7% (24/313)	6.3% (7/112)	0.832**
Non-TLR, CABG	0.3% (1/321)	0.0% (0/113)	1.000**	1.0% (3/313)	0.0% (0/112)	0.570**
SAFETY						
Total Death	0.6% (2/321)	0.0% (0/113)	1.000**	1.6% (5/313)	4.5% (5/112)	0.138**
Cardiac Death	0.0% (0/321)	0.0% (0/113)	--	0.0% (0/313)	0.9% (1/112)	0.264**
Non-Cardiac Death	0.6% (2/321)	0.0% (0/113)	1.000**	1.6% (5/313)	3.6% (4/112)	0.252**
Cardiac Death or MI	0.6% (2/321)	3.5% (4/113)	0.042**	0.6% (2/313)	3.6% (4/112)	0.044**
MI	0.6% (2/321)	3.5% (4/113)	0.042**	0.6% (2/313)	3.6% (4/112)	0.044**
Q wave MI	0.0% (0/321)	0.0% (0/113)	--	0.0% (0/313)	0.0% (0/112)	--
Non-Q wave MI	0.6% (2/321)	3.5% (4/113)	0.042**	0.6% (2/313)	3.6% (4/112)	0.044**
Stent Thrombosis (protocol)	0.0% (0/321)	0.0% (0/113)	--	0.0% (0/313)	0.0% (0/112)	--

** P-values for outcome differences are not adjusted for multiple comparisons.

Notes:

Fisher's Exact test was used for P-values.

This trial was not adequately powered to compare the rate of low frequency events, nor was it sized to determine the rate of low frequency events with a pre-specified precision.

Numbers are % (Count/Sample Size).

To be included in the event rate calculation for a given interval, a patient either had to have an event before the time of interest or they had to be event-free before the lower window of the follow-up.

Table 20: ENDEAVOR III Protocol-Defined Stent Thrombosis* Through 24 Months

	Endeavor (N = 323)	Cypher (N = 113)	P-Value
Cumulative ST through 24 Months	0.0% (0/313)	0.0% (0/112)	--
Acute ST (≤ 24 hrs)	0.0% (0/323)	0.0% (0/113)	--
Subacute ST (> 24 hrs and ≤ 30 days)	0.0% (0/323)	0.0% (0/113)	--
Late ST (> 30 days and ≤ 12 months)	0.0% (0/320)	0.0% (0/112)	--
Very late ST (> 12 months and ≤ 24 months)	0.0% (0/313)	0.0% (0/112)	--

* See section XI.F1 for the per protocol stent thrombosis definition.
Notes:
This trial was not adequately powered to compare the rate of low frequency events, nor was it sized to determine the rate of low frequency events with a pre-specified precision.
To be included in the event rate calculation for a given interval, a patient either had to have an event before the time of interest or they had to be event-free before the lower window of the follow-up.
Numbers are % (Count/Sample Size).

C. Results of the ENDEAVOR II Clinical Trial

Primary Objective: To demonstrate superiority in the safety and efficacy of the Endeavor Zotarolimus-Eluting Coronary Stent System when compared to the Driver Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries with a reference vessel diameter of 2.25 mm to 3.5 mm in diameter and lesion lengths of ≥ 14 mm and ≤ 27 mm.

Design: This was a prospective, multi-center, double-blind, two-arm randomized and controlled superiority trial that compared the Endeavor stent to a control bare metal stent (BMS), the Driver stent. A total of 1197 patients were enrolled at 72 study sites in Asia, Australia, Europe, Israel and New Zealand who presented with symptomatic ischemic heart disease attributable to stenotic lesions of native coronary arteries that were amenable to treatment by stenting. Patients were randomized to receive either an Endeavor or a Driver stent in a 1:1 ratio. Multiple stents were allowed for bailout only.

Follow-up was performed at 30 days, 6, 8, 9, 12 months, at 2 and 3 years, and will be performed annually thereafter out to 5 years. The first 600 consecutively enrolled patients (across all sites) were scheduled to receive angiographic evaluation at 8 months, and 300 patients were scheduled to receive IVUS evaluation at 8 months at pre-specified sites. Following the index procedure, patients were treated with aspirin indefinitely and clopidogrel or ticlopidine for a minimum of 3 months.

Demographics: The mean age was 61.6 years for patients in the Endeavor arm and 61.9 years for patients in the Driver arm. The Endeavor arm had 77.2% (461/597) males, and the Driver arm had 75.3% (449/596) males. In the Endeavor arm, 21.7% (129/595) of patients had prior percutaneous coronary revascularization, compared to 18.0% (107/594) of patients in the Driver arm. In the Endeavor arm, 18.2% (108/595) of patients had a history of diabetes mellitus, compared to 22.2% (132/595) of patients in the Driver arm. Patients were well matched for baseline demographics, with no statistically significant differences between treatment arms.

Results: The primary and secondary endpoints, protocol-defined stent thrombosis, and the latest available follow-up results are presented below (Table 21, Table 22, Table 23 and Figure 4).

The primary endpoint of TVF at 9 months was met with 7.9% (47/592) for the Endeavor arm and 15.1% (89/591) for the Driver arm ($p < 0.001$ for superiority).

The pre-specified secondary endpoint of in-segment late loss at 8 months was met, with measurements of 0.36 mm ± 0.46 mm (264) for the Endeavor arm and 0.72 mm ± 0.61 mm (263) for the Driver arm ($p < 0.001$ for superiority).

Table 21: ENDEAVOR II Clinical Results

	Outcomes at 9 Months			Outcomes at 36 Months (latest available follow-up)		
	Endeavor (N = 598)	Driver (N = 599)	P-Value	Endeavor (N = 598)	Driver (N = 599)	P-Value
PRIMARY ENDPOINT						
TVF§	7.9% (47/592)	15.1% (89/591)	< 0.001*	12.8% (74/577)	21.4% (124/579)	< 0.001**
§ 9-month primary endpoint. * Test for superiority.						
EFFICACY						
TVR	5.6% (33/592)	12.5% (74/591)	< 0.001**	9.5% (55/577)	17.6% (102/579)	< 0.001**
TLR	4.6% (27/592)	11.8% (70/591)	< 0.001**	7.3% (42/577)	14.7% (85/579)	< 0.001**
TLR, PCI	4.2% (25/592)	11.3% (67/591)	< 0.001**	6.9% (40/577)	13.8% (80/579)	< 0.001**
TLR, CABG	0.3% (2/592)	0.5% (3/591)	0.687**	0.5% (3/577)	1.0% (6/579)	0.506**
Non-TLR	1.5% (9/592)	2.2% (13/591)	0.400**	2.9% (17/577)	4.8% (28/579)	0.128**
Non-TLR, PCI	1.4% (8/592)	2.2% (13/591)	0.282**	2.8% (16/577)	4.7% (27/579)	0.119**
Non-TLR, CABG	0.2% (1/592)	0.0% (0/591)	1.000**	0.2% (1/577)	0.3% (2/579)	1.000**
SAFETY						
Total Death	1.2% (7/592)	0.5% (3/591)	0.342**	3.3% (19/577)	4.5% (26/579)	0.362**
Cardiac Death	0.8% (5/592)	0.5% (3/591)	0.726**	1.6% (9/577)	2.4% (14/579)	0.400**
Non-Cardiac Death	0.3% (2/592)	0.0% (0/591)	0.500**	1.7% (10/577)	2.1% (12/579)	0.830**
Cardiac Death or MI	3.4% (20/592)	4.4% (26/591)	0.372**	4.5% (26/577)	6.7% (39/579)	0.125**
MI	2.7% (16/592)	3.9% (23/591)	0.260**	3.3% (19/577)	4.3% (25/579)	0.443**
Q wave MI	0.3% (2/592)	0.8% (5/591)	0.287**	0.3% (2/577)	1.0% (6/579)	0.287**
Non-Q wave MI	2.4% (14/592)	3.0% (18/591)	0.481**	2.9% (17/577)	3.3% (19/579)	0.866**
Stent Thrombosis (protocol)	0.5% (3/592)	1.2% (7/591)	0.224**	0.5% (3/577)	1.2% (7/579)	0.342**

** P-values for outcome differences are not adjusted for multiple comparisons.

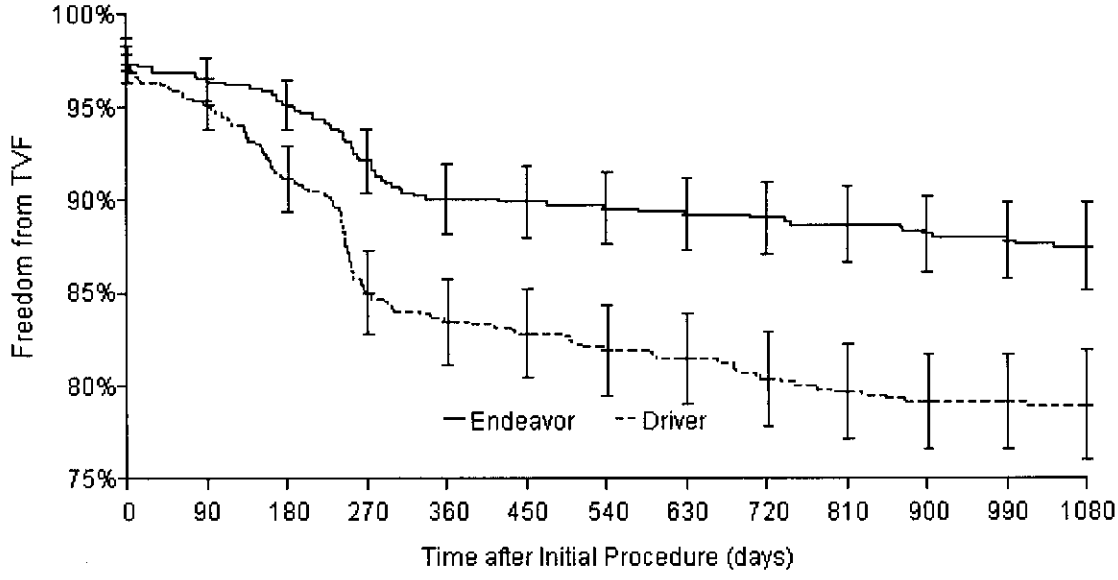
Notes:

Fisher's Exact test was used for P-values.

This trial was not adequately powered to compare the rate of low frequency events, nor was it sized to determine the rate of low frequency events with a pre-specified precision.

Numbers are % (Count/Sample Size).

To be included in the event rate calculation for a given interval, a patient either had to have an event before the time of interest or they had to be event-free before the lower window of the follow-up.



TVF	Event free	Event Rate	P-Value*
Endeavor	87.4%	12.6%	< 0.001
Driver	78.9%	21.1%	

* Log-rank P-value. P-value is not adjusted for multiple comparisons.

Figure 4: Survival Free from Target Vessel Failure (at 1080 days)

Table 22: Endeavor II 8-Month Angiographic and IVUS Results

	Endeavor (N = 598)	Driver (N = 599)	P-Value
SECONDARY ENDPOINT			
Late Loss, In-segment (mm)¥	0.36 ± 0.46 (264)	0.72 ± 0.61 (263)	< 0.001*
¥ Powered secondary endpoint. * test for superiority.			
OTHER ANGIOGRAPHIC RESULTS			
MLD (mm), In-stent			
Post-Procedure	2.59 ± 0.43 (588)	2.61 ± 0.44 (589)	0.436**
8-Month	1.99 ± 0.56 (264)	1.62 ± 0.70 (265)	< 0.001**
MLD (mm), In-segment			
Post-Procedure	2.21 ± 0.49 (589)	2.24 ± 0.49 (590)	0.302**
8-Month	1.86 ± 0.55 (264)	1.56 ± 0.67 (265)	< 0.001**
% DS, In-stent			
Post-Procedure	6.04 ± 10.43 (588)	6.23 ± 10.03 (589)	0.757**
8-Month	27.91 ± 17.30 (264)	42.24 ± 21.73 (265)	< 0.001**
% DS, In-segment			
Post-Procedure	20.39 ± 10.26 (589)	20.11 ± 9.38 (590)	0.622**
8-Month	32.67 ± 16.27 (264)	44.33 ± 20.45 (265)	< 0.001**
Late Loss, In-stent (mm)	0.62 ± 0.46 (264)	1.03 ± 0.59 (263)	< 0.001**
Binary Restenosis			
In-stent Restenosis	9.5% (25/264)	33.2% (88/265)	< 0.001**
In-segment Restenosis	13.3% (35/264)	34.7% (92/265)	< 0.001**
IVUS RESULTS			
Neointimal Volume (mm^3)	30.15 ± 21.66 (90)	53.51 ± 39.80 (81)	< 0.001**
% Volume Obstruction	17.34 ± 10.27 (90)	29.55 ± 17.58 (81)	< 0.001**
Incomplete Apposition			
Post-procedure	24.8% (36/145)	19.6% (28/143)	0.322**
8-Month	16.8% (21/125)	14.5% (16/110)	0.721**
Resolved	7.0% (8/114)	6.7% (7/104)	1.000**
Persistent	17.5% (20/114)	14.4% (15/104)	0.583**
Late Acquired	0.0% (0/114)	0.0% (0/104)	--

** P-values for outcome differences are not adjusted for multiple comparisons.
Note:
Fisher's Exact test or Student's t-test was used for P-values.

Table 23: ENDEAVOR II Protocol-Defined Stent Thrombosis* Through 36 Months

	Endeavor (N = 598)	Driver (N = 599)	P-Value
Cumulative ST through 36 Months	0.5% (3/577)	1.2% (7/579)	0.342**
Acute ST (≤ 24 hrs)	0.2% (1/596)	0.2% (1/594)	1.000**
Subacute ST (> 24 hrs and ≤ 30 days)	0.3% (2/596)	1.0% (6/594)	0.178**
Late ST (> 30 days and ≤ 12 months)	0.0% (0/590)	0.0% (0/589)	--
Very late ST (> 12 months and ≤ 36 months)	0.0% (0/577)	0.0% (0/579)	--

* See section XI.F1for the per protocol stent thrombosis definition.
** P-values for outcome differences are not adjusted for multiple comparisons.
Notes:
Fisher's Exact test was used for P-values.
This trial was not adequately powered to compare the rate of low frequency events, nor was it sized to determine the rate of low frequency events with a pre-specified precision.
To be included in the event rate calculation for a given interval, a patient either had to have an event before the time of interest or they had to be event-free before the lower window of the follow-up.
Numbers are % (Count/Sample Size).

D. Results of the ENDEAVOR I Clinical Trial

Primary Objective: To demonstrate the safety and efficacy of the Endeavor Zotarolimus-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries with a reference vessel diameter of 3.0 mm to 3.5 mm and lesion length of ≤ 15 mm.

Design: The ENDEAVOR I trial was the first-in-man study for the Endeavor stent. This was a non-randomized, prospective, multi-center, single-arm trial. A total of 100 patients were enrolled at 8 study sites in Australia and New Zealand who presented with symptomatic ischemic heart disease attributable to stenotic lesions of the native coronary arteries that were amenable to treatment by stenting.

Follow-up was performed at 30 days, 4, 9, 12 months, at 2, 3 and 4 years, and will be performed at 5 years. All patients were scheduled to have angiographic follow-up at 4 and 12 months. Following the index procedure, patients were treated with aspirin indefinitely and clopidogrel for a minimum of 3 months.

Demographics: The mean age was 59 years, and 79% were male. Diabetes was present in 16%, and 47% had a prior MI.

Results: The primary and secondary endpoint, protocol-defined stent thrombosis, and the latest available follow-up results are presented below (Table 24, Table 25, and Table 26).

The primary endpoint of 30-day MACE was 1.0% (1/100), and the co-primary endpoint of in-segment late loss at 4 months was 0.22 ± 0.43 mm (98).

Table 24: ENDEAVOR I Clinical Results

	Endeavor (N = 100)	Endeavor (N = 100)
PRIMARY ENDPOINT		
MACE at 30 days[§]	1.0% (1/100)	
[§]30 day primary endpoint.		
	Outcomes at 9 Months	**Outcomes at 48 Months (latest available follow-up)**
EFFICACY		
TVF	2.0% (2/100)	5.2% (5/97)
TVR	2.0% (2/100)	5.2% (5/97)
TLR	2.0% (2/100)	3.1% (3/97)
TLR, PCI	2.0% (2/100)	3.1% (3/97)
TLR, CABG	1.0% (1/100)	1.0% (1/97)
Non-TLR	0.0% (0/100)	2.1% (2/97)
Non-TLR, PCI	0.0% (0/100)	1.0% (1/97)
Non-TLR, CABG	0.0% (0/100)	1.0% (1/97)
SAFETY		
Total Death	0.0% (0/100)	4.1% (4/97)
Cardiac Death	0.0% (0/100)	0.0% (0/97)
Non-Cardiac Death	0.0% (0/100)	4.1% (4/97)
Cardiac Death or MI	1.0% (1/100)	1.0% (1/97)
MI	1.0% (1/100)	1.0% (1/97)
Q wave MI	0.0% (0/100)	0.0% (0/97)
Non-Q wave MI	1.0% (1/100)	1.0% (1/97)
Stent Thrombosis (protocol)	1.0% (1/100)	1.0% (1/97)

Notes:
Numbers are % (Count/Sample Size).
This trial was not adequately powered to compare the rate of low frequency events, nor was it sized to determine the rate of low frequency events with a pre-specified precision.
To be included in the event rate calculation for a given interval, a patient either had to have an event before the time of interest or they had to be event-free before the lower window of the follow-up.

Table 25: ENDEAVOR I 12- Month Angiographic and IVUS Results

	Endeavor (N = 100)
PRIMARY ENDPOINT	
In-segment Late loss at 4 Months (mm) §	0.22 ± 0.43(98)
§ 4-month primary endpoint	
ANGIOGRAPHIC RESULTS	
MLD (mm), In-stent	
Post-Procedure	2.84 ± 0.35 (100)
12-Month	2.26 ± 0.49 (92)
MLD (mm), In-segment	
Post-Procedure	2.52 ± 0.42 (100)
12-Month	2.08 ± 0.47 (92)
% DS, In-stent	
Post-Procedure	5.37 ± 7.51 (100)
12-Month	21.75 ± 15.35 (92)
% DS, In-segment	
Post-Procedure	16.54 ± 8.40 (100)
12-Month	28.00 ± 13.41 (92)
Late Loss, In-stent (mm)	0.58 ± 0.44 (92)
Late Loss, In-segment (mm)	0.43 ± 0.44 (92)
Binary Restenosis	
In-stent Restenosis	4.3% (4/92)
In-segment Restenosis	5.4% (5/92)
IVUS RESULTS	
Neointimal Volume (mm^3)	14.15 ±11.82 (86)
% Volume Obstruction	9.73 ±8.50 (86)
Incomplete Apposition	
Post-procedure	12.6% (12/95)
12-Month	4.7% (4/86)
Resolved	8.1% (7/86)
Persistent	4.7% (4/86)
Late Acquired	0.0% (0/86)

Table 26: ENDEAVOR I Protocol-Defined Stent Thrombosis* Through 48 Months

	Endeavor I (N = 100)
Cumulative ST through 48 Months	1.0% (1/97)
Acute ST (≤ 24 hrs)	0.0% (0/100)
Subacute ST (> 24 hrs and ≤ 30 days)	1.0% (1/100)
Late ST (> 30 days and ≤ 12 months)	0.0% (0/99)
Very Late ST (> 12 months and ≤ 48 months)	0.0% (0/97)

* See section XI.F1for the per protocol stent thrombosis definition.
Notes:
To be included in the event rate calculation for a given interval, a patient either had to have an event before the time of interest or they had to be event-free before the lower window of the follow-up.
Numbers are % (Count/Sample Size).

E. Gender Bias

The gender selection in this series of clinical trials was completely random, and solely based upon exclusion and inclusion criteria. In the ENDEAVOR IV study (conducted in the US), women represented 32.3% of the population. In the ENDEAVOR III study (conducted in the US), women represented 30.5% of the population. In the ENDEAVOR II study (conducted OUS), women represented 23.7% of the population. In the ENDEAVOR I feasibility trial (conducted OUS), women represented 21.0% of the population. According to the American Heart Association Heart Disease and Stroke Statistics (2008 Update), women represent approximately 40% of patients age 60-79 with coronary heart disease. Although the ratio of men to women in the ENDEAVOR trials does not match the prevalence of coronary artery disease in the general U.S. population, it is reflective of the underlying distribution of the disease for the types of patients that would meet the study inclusion/exclusion criteria (i.e., younger, less complex disease). No selection bias on the basis of gender was identified during the review. In addition, data were analyzed to determine if gender was an independent predictor of clinical outcomes of death, cardiac death, all MI, QMI, Non-Q MI, cardiac death or MI, TVF, TVR, TLR and stent thrombosis (all definitions). No differences in safety or effectiveness were found, with respect to gender.

F. Overall Results of the Endeavor Clinical Program (ENDEAVOR I, II, II-CA, III, IV and USPK)

In order to better estimate the incidence of low-frequency events or outcomes in various specific patient subgroups, a patient-level pooled analysis was conducted. This analysis compared pooled Endeavor stent patients (across all trials) to Driver stent patients from ENDEAVOR II. Although ENDEAVOR I (100), ENDEAVOR II-CA (296) and ENDEAVOR USPK (43) are not randomized trials, for the purpose of this analysis, they are pooled with the randomized trials -- ENDEAVOR II (596), ENDEAVOR III (323) and ENDEAVOR IV (770) -- to allow the broadest comparison of the Endeavor stent (1287 patients) vs. the Driver stent patients (599) to 2 years of follow-up. Across the ENDEAVOR program, 2133 patients received the Endeavor stent. The patient-level data

was included until the latest available time point depending on the follow-up status for each trial -- ENDEAVOR I (97% complete at 4 years), ENDEAVOR II (97.8% completed at 3 years), ENDEAVOR II-CA (97.3% complete at 2 years), ENDEAVOR III (96.9% complete at 2 years), ENDEAVOR IV (96.1% complete at 9 months), and ENDEAVOR USPK (97.7% complete at 9 months).

Table 27: Patient Follow-up

	30 Days	6 Months	9 Months	12 Months	24 Months	36 Months	48 Months
ENDEAVOR I	100	100	100	99	99	98	97
ENDEAVOR II	596	593	592	590	587	577	-
ENDEAVOR II CA	296	295	293	292	288	-	-
ENDEAVOR III	323	321	321	320	313	-	-
ENDEAVOR IV	770	766	740	-	-	-	-
ENDEAVOR PK	43	43	42	-	-	-	-
Total	**2128**	**2118**	**2088**	**1301**	**1287**	**675**	**97**

It is acknowledged that the results of such retrospective pooled analyses are hypothesis-generating in nature. Definitive proof of the presence or absence of any differences between sub-groups requires prospectively powered assessment in dedicated clinical trials.

The results of the pooled analysis show the Endeavor stent significantly reduces the need for repeat revascularization vs. the Driver stent that is maintained throughout long-term follow-up as shown in Figure 5.

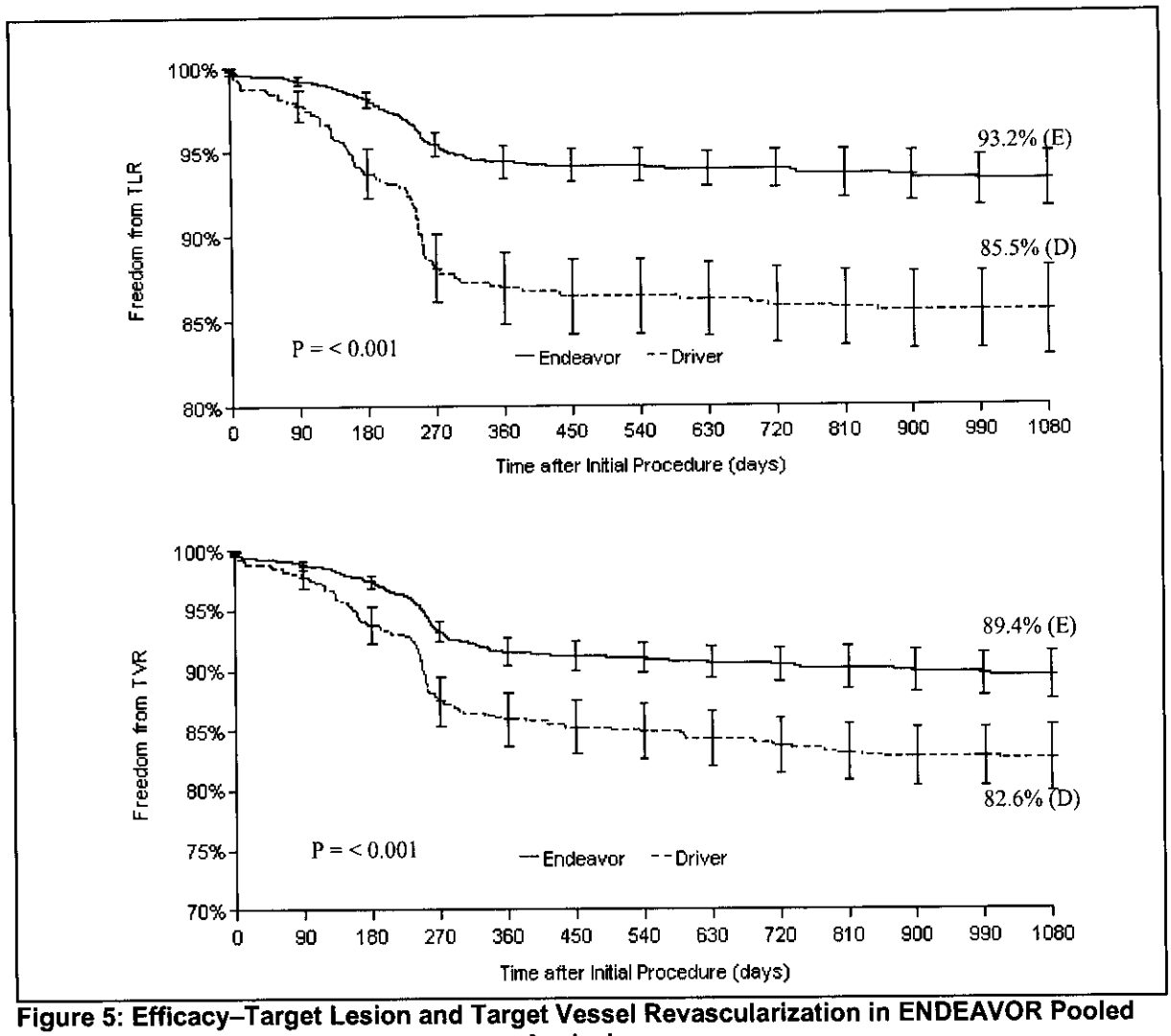


Figure 5: Efficacy–Target Lesion and Target Vessel Revascularization in ENDEAVOR Pooled Analysis

Kaplan-Meier rates %.
P-values are from the Log-rank test and are not adjusted for multiple comparisons.

The Endeavor stent is more effective than the Driver stent in reducing the need for revascularization, as shown in Figure 5. The analyses shown in Figure 6 suggest a lower rate of cardiac death in pooled Endeavor patients compared to Driver patients from ENDEAVOR II. The pooled analysis addressed total death as well as cardiac death and non-cardiac death as its components. There were no differences noted in non-cardiac or total death between groups.

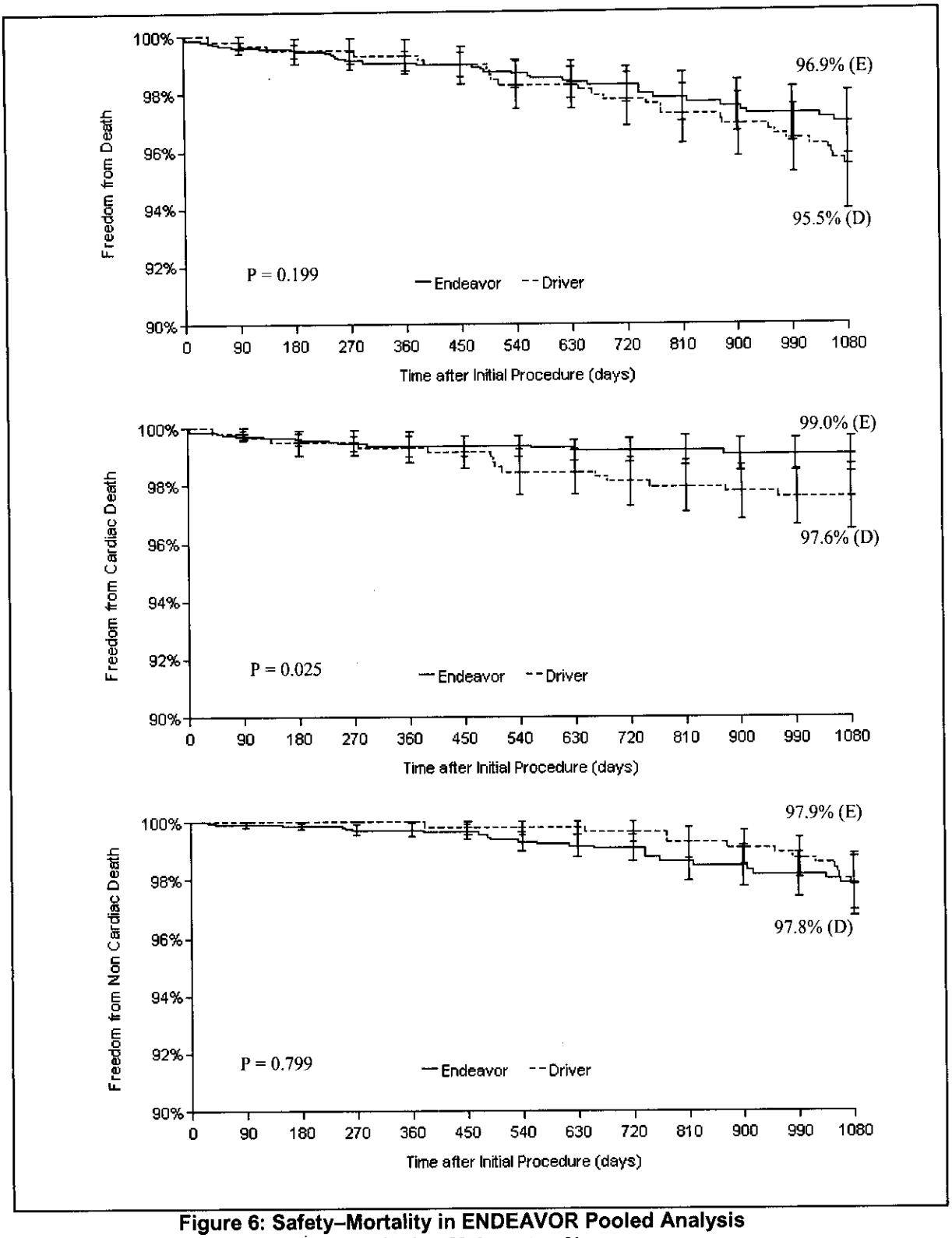


Figure 6: Safety–Mortality in ENDEAVOR Pooled Analysis Kaplan-Meier rates %.

P-values are from the Log-rank test and are not adjusted for multiple comparisons.

The MI rates in patients receiving the Endeavor stent vs. the Driver control stent were also examined. At three years, any differences noted favored the Endeavor stent as shown in Figure 7.

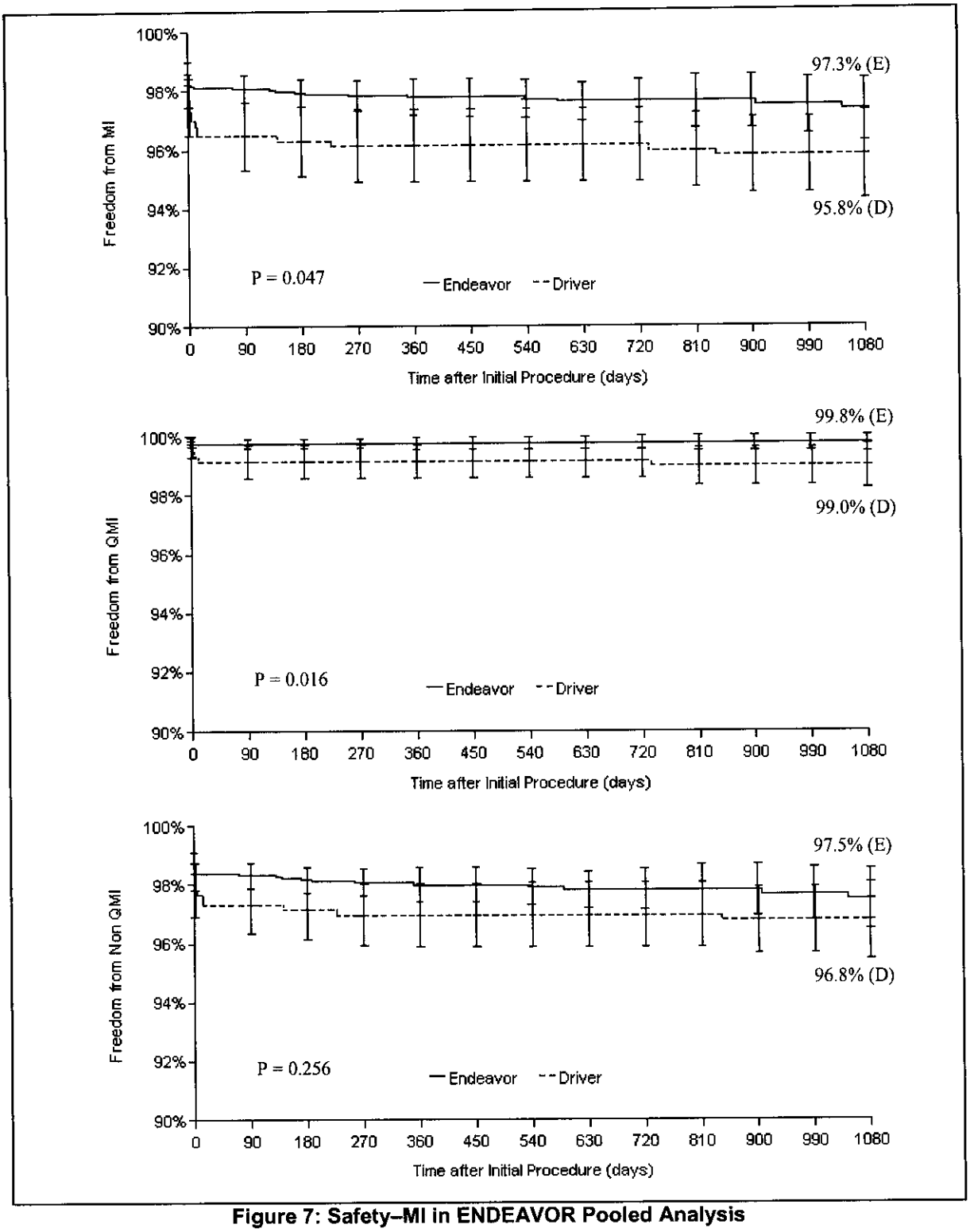


Figure 7: Safety–MI in ENDEAVOR Pooled Analysis

Kaplan-Meier rates %.
P-values are from the Log-rank test and are not adjusted for multiple comparisons.

1. **Stent Thrombosis in Endeavor Pooled Analysis**

For the critical safety endpoint of stent thrombosis, Endeavor rates have been reported using two different reporting mechanisms: the pre-specified protocol definition and the retrospective Academic Research Consortium (ARC)[1] definition. Stent thrombosis was defined (per protocol) in the ENDEAVOR clinical trials as the occurrence of any of the following:

- Angiographic thrombus or subacute closure within the stented vessel at the time of the clinically-driven angiographic restudy for documented ischemia (chest pain and ECG changes).
- Any death not attributed to a non-cardiac cause within the first 30 days.
- Late stent thrombosis is reported according to the following criteria: MI > 30 days after index and attributable to the target vessel, angiographic documentation (site-reported or by QCA) of thrombus or total occlusion at the target site and freedom from interim revascularization of the target vessel.

All events were re-adjudicated based on FDA recommendation using the ST definitions proposed by ARC. This was performed by an independent events committee blinded to the treatment groups of the individual patients. According to ARC, each incident of ST is categorized by timing, level of evidence, and relationship to TLR as follows:

Timing:
Acute stent thrombosis[2]: 0–24 hours post stent implantation
Subacute stent thrombosis[2]: > 24 hours–30 days post stent implantation
Late stent thrombosis: > 30 days–1 year post stent implantation
Very late stent thrombosis: > 1 year post stent implantation

Level of Evidence:

- Definite stent thrombosis: Definite stent thrombosis is considered to have occurred by either angiographic or pathologic confirmation.
- Probable stent thrombosis: Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:
  - Any unexplained death within the first 30 days
  - Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause
- Possible stent thrombosis: Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days following intracoronary stenting until end of trial follow-up.

Stent Thrombosis After TLR: Censored vs. Non-Censored:

- Censoring stent thrombosis events that occur post-TLR performed for stent restenosis may be appropriate, as the thrombosis may be related to the treatment chosen to treat restenosis (e.g., brachytherapy) rather than the type of stent used in the index procedure. Alternatively, censoring stent thrombosis events that occur after TLR may bias results in favor of devices with higher restenosis risks. Therefore, stent thrombosis data presented in this review will report both TLR-censored and TLR-uncensored rates as follows:

  - ARC Definite + probable (TLR-censored): Adjudicated stent thrombosis meeting the definite or probable ARC definition with censoring of any definite or probable stent thrombosis events that may have occurred after a TLR.
  - ARC Definite + probable (TLR-uncensored): Adjudicated stent thrombosis meeting the definite or probable ARC definition including any definite or probable stent thrombosis events that may have occurred after a TLR.

In the ENDEAVOR clinical program comprised of six multi-center trials, 2133 patients were assigned to receive the Endeavor Stent (1287 patients were followed out to two years and 675 patients out to three years). When all patients who received the Endeavor stent across trials were pooled and compared to the patients who received the Driver stent in ENDEAVOR II, the Endeavor stent did not appear to pose an increased stent thrombosis risk. Regardless of the method for reporting the pre-specified protocol definition or the retrospective ARC definition, in the randomized ENDEAVOR II trial and the FDA-requested pooled analysis, the Endeavor stent exhibited low event rates that were similar to or lower than the Driver stent.

The cumulative rates of stent thrombosis (per protocol and per the ARC definite + probable definitions) in patients treated with Endeavor stents from the pooled ENDEAVOR trials are shown in Table 28 below. (Stent thrombosis rates observed in patients treated with Driver stents in ENDEAVOR II are shown for reference.) ARC definite + probable stent thrombosis is reported both as TLR-censored and uncensored.

Table 28: Stent Thrombosis (Protocol) and Definite + Probable Stent Thrombosis (ARC)

	Endeavor (N=2132)	95% CI	Driver (N=596)	95% CI
Thrombosis (0-30 Days)				
Stent Thrombosis (Protocol)	0.3% (7/2128)	[0.1%, 0.7%]	1.2% (7/594)	[0.5%, 2.4%]
ARC Definite + Probable (TLR-censored)	0.3% (7/2128)	[0.1%, 0.7%]	1.2% (7/594)	[0.5%, 2.4%]
ARC Definite + Probable (TLR-uncensored)	0.3% (7/2128)	[0.1%, 0.7%]	1.2% (7/594)	[0.5%, 2.4%]
Thrombosis (0-6 Months)				
Stent Thrombosis (Protocol)	0.5% (10/2118)	[0.2%, 0.9%]	1.2% (7/593)	[0.5%, 2.4%]
ARC Definite + Probable (TLR-censored)	0.5% (11/2118)	[0.3%, 0.9%]	1.2% (7/593)	[0.5%, 2.4%]
ARC definite + probable (TLR-uncensored)	0.5% (11/2118)	[0.3%, 0.9%]	1.2% (7/593)	[0.5%, 2.4%]
Thrombosis (0-12 Months)				
Stent Thrombosis (Protocol)	0.3% (4/1301)	[0.1%, 0.8%]	1.2% (7/589)	[0.5%, 2.4%]
ARC Definite + Probable (TLR-censored)	0.4% (5/1301)	[0.1%, 0.9%]	1.4% (8/589)	[0.6%, 2.7%]
ARC Definite + Probable (TLR-uncensored)	0.5% (6/1301)	[0.2%, 1.0%]	1.4% (8/589)	[0.6%, 2.7%]
Thrombosis (0-24 Months)				
Stent Thrombosis (Protocol)	0.3% (4/1287)	[0.1%, 0.8%]	1.2% (7/586)	[0.5%, 2.4%]
ARC Definite + Probable (TLR-censored)	0.5% (6/1287)	[0.2%, 1.0%]	1.4% (8/586)	[0.6%, 2.7%]
ARC Definite + Probable (TLR-uncensored)	0.5% (7/1287)	[0.2%, 1.1%]	1.4% (8/586)	[0.6%, 2.7%]
Thrombosis (0-36 Months)				
Stent Thrombosis (Protocol)	0.6% (4/675)	[0.2%, 1.5%]	1.2% (7/579)	[0.5%, 2.5%]
ARC Definite + Probable (TLR-censored)	0.9% (6/675)	[0.3%, 1.9%]	1.4% (8/579)	[0.6%, 2.7%]
ARC Definite + Probable (TLR-uncensored)	0.9% (6/675)	[0.3%, 1.9%]	1.6% (9/579)	[0.7%, 2.9%]

Beyond one year, the Endeavor stent showed zero stent thrombosis by the pre-specified protocol definition and one stent thrombosis event by the *post hoc* ARC definition (definite + probable).

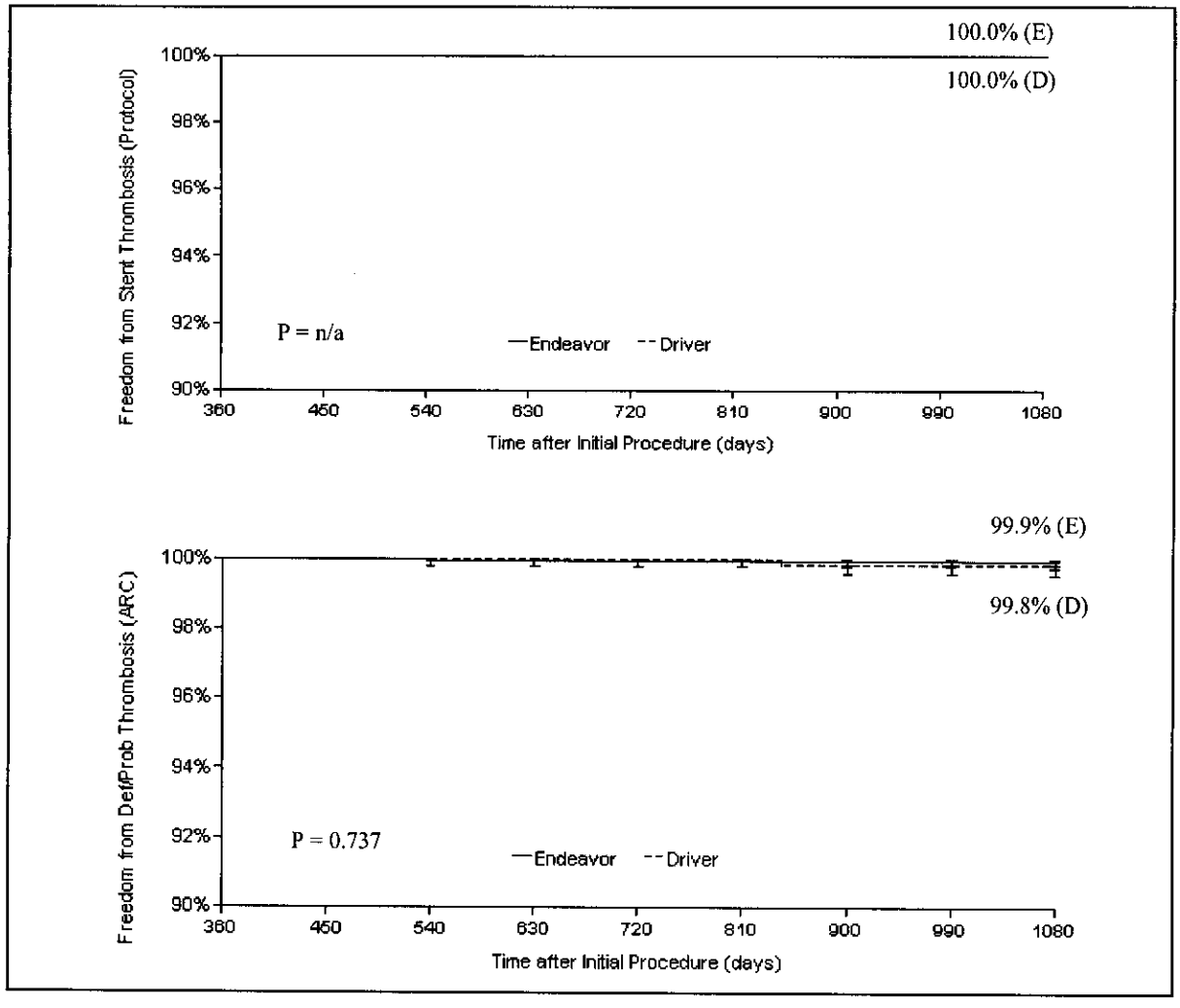


Figure 8: Freedom from Stent Thrombosis (Protocol) and Definite/Probable Thrombosis (ARC)
Kaplan-Meier rates %.
P-values are from the Log-rank test and are not adjusted for multiple comparisons.

2. Diabetic Patients in ENDEAVOR Pooled Analysis

Diabetic patients comprise an important patient subgroup that is at increased risk for cardiovascular morbidity and mortality. Although diabetic patients were included in the Endeavor clinical trials, there were no pre-specified hypotheses or trial design features to warrant a specific labeled indication for the use of the Endeavor stent in diabetic individuals.

Table 29 shows clinical outcomes through 9 months in patients pooled from the ENDEAVOR trials and stratified by non-diabetics, all diabetics, insulin-dependent diabetics, and non-insulin dependent diabetics. As expected, TLR and TVR rates were numerically increased in diabetics vs. non-diabetics, with no observed safety signals with respect to the rates of death, cardiac death, MI, or stent thrombosis.

Table 29: Clinical Events Through 9 Months

	Non-Diabetics N = 1549	All Diabetics N = 537	Insulin-Dependent N = 154	Non-Insulin-Dependent N = 381
Death	0.8%	0.8%	0.7%	0.8%
Cardiac Death	0.5%	0.6%	0.0%	0.8%
MI	2.4%	1.5%	2.0%	1.4%
Cardiac Death or MI	2.8%	1.9%	2.0%	1.9%
Protocol ST	0.5%	0.6%	0.7%	0.5%
Definite and Probable ST ARC (TLR-censored)	0.5%	0.8%	1.3%	0.5%
Definite and Probable ST ARC (TLR-uncensored)	0.5%	0.8%	1.3%	0.5%
TLR	4.1%	6.3%	6.0%	6.5%
TVR	5.8%	9.4%	8.0%	9.8%

From the pooled ENDEAVOR studies, clinical outcomes through 9 months are shown in Table 30 stratified by all diabetics, insulin-dependent diabetics, and non-insulin dependent diabetics. Event rates for the Driver patients in the ENDEAVOR II study are shown for reference. These data show no observed safety signals with respect to the rates of death, cardiac death, MI, or stent thrombosis with the Endeavor stent compared to the Driver stent.

Table 30: Clinical Events in Diabetics (Endeavor Compared to Driver BMS) Through 9 Months

	All Diabetics		Insulin-Dependent		Non-Insulin-Dependent	
	Endeavor N = 537	Driver N = 132	Endeavor N = 154	Driver N = 44	Endeavor N = 381	Driver N = 88
Death	0.8%	1.5%	0.7%	2.3%	0.8%	1.1%
Cardiac Death	0.6%	1.5%	0.0%	2.3%	0.8%	1.1%
MI	1.5%	3.8%	2.0%	2.3%	1.4%	4.5%
Cardiac Death or MI	1.9%	5.3%	2.0%	4.5%	1.9%	5.7%
Protocol ST	0.6%	2.3%	0.7%	0.0%	0.5%	3.4%
Definite and Probable ST ARC (TLR-censored)	0.8%	2.3%	1.3%	0.0%	0.5%	3.4%
Definite and Probable ST ARC (TLR-uncensored)	0.8%	2.3%	1.3%	0.0%	0.5%	3.4%
TLR	6.3%	15.2%	6.0%	13.6%	6.5%	15.9%
TVR	9.4%	15.9%	8.0%	13.6%	9.8%	17.0%

XII. Conclusions Drawn from the Studies

The safety and effectiveness of the Endeavor Zotarolimus-Eluting Coronary Stent System are based on the results obtained from: biocompatibility; *in vivo* pharmacokinetics; *in vitro* engineering testing; coating characterization; chemistry, manufacturing and controls information; *in vivo* animal testing; sterilization and stability testing; and clinical studies. These test results revealed the following:

The biocompatibility, *in vivo* pharmacokinetics, and *in vivo* animal testing that were conducted demonstrated that the acute and chronic *in vivo* performance characteristics of the product provide reasonable assurance of safety and are acceptable for clinical use.

The *in vitro* engineering testing conducted on the stent and delivery system(s) demonstrated that the performance characteristics met the product specifications and the coating characterization testing adequately described the important attributes of the zotarolimus/polymer coating. The chemistry, manufacturing, and controls information ensures that product meeting specifications will be released.

The test results obtained from the sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. The stability testing demonstrated that the product can be labeled with a shelf life of 12 months.

The clinical testing conducted demonstrated that the product provides a reasonable assurance of safety and effectiveness when used as indicated in accordance with the instructions for use. Specifically, the Endeavor stent was shown to be superior to an approved bare metal stent with respect to both clinical outcomes and angiographic data. In addition, clinical outcomes with the Endeavor stent were non-inferior to those obtained using an approved drug-eluting stent. Although the Endeavor stent did not demonstrate non-inferiority to two approved drug-eluting stents based on angiographic data, the aggregate of clinically relevant safety and effectiveness data outweighed the results of surrogate angiographic measurements.

XIII. Panel Recommendation

At an advisory meeting held on October 10, 2007, the Circulatory Systems Devices Panel unanimously recommended that Medtronic's PMA for the Endeavor Zotarolimus Drug-Eluting Coronary Stent System & Over-the-Wire (OTW), Rapid Exchange (RX), and Multi-Exchange II (MX^2) Stent Delivery Systems be approved subject to submission, and approval by, the Center for Devices and Radiological Health (CDRH) of the following:

1. The sponsor should conduct a $\geq$ 5,000 patient single-arm post-approval study with endpoints of very late stent thrombosis and cardiac death + myocardial infarction, rigorous monitoring, and follow-up through at least 5 years.
2. The labeling regarding antiplatelet therapy use should be consistent with current ACC/AHA Guidelines as FDA has proposed for currently approved drug-eluting stents following the December 2006 panel meeting. Specifically, the labeling should describe the use of antiplatelet therapy in the clinical trials and suggest that use through 1 year may be beneficial per the published consensus guidelines.

XIV. CDRH Decision

CDRH concurred with the Panel's recommendations of October 10, 2007.

Medtronic's post-approval study proposal developed with FDA and presented to the Panel addresses the Panel's first recommendation. Specifically, data from 5,300 Endeavor patients (2,000 from the US registry and 3,300 OUS from the Endeavor arm of the PROTECT study) will be collected and pooled for an analysis of rates of stent thrombosis and cardiac death plus myocardial infarction. Data will be analyzed separately for the patients enrolled in accordance with the labeled indication and collectively for all patients enrolled in the studies.

Medtronic expects the PROTECT trial and the U.S. Post Approval Registry will include a sufficient number of patients who have received the Endeavor stent in accordance with the approved indication to allow evaluation of both endpoints noted above. Data from at least 2000 patients will be available to provide 80% power to demonstrate that the rate of stent thrombosis per year is $< 1.0\%$ in Endeavor patients who receive the Endeavor stent in accordance with the approved indication. This sample size also provides $\geq 80\%$ power to demonstrate that the rate of cardiac death + myocardial infarction at annual timepoints through 5 years in Endeavor-stented patients is less than the incidence in patients who received the Driver stent in the ENDEAVOR II trial plus a 50% non-inferiority margin.

To address the Panel's second recommendation, Medtronic provided revised labeling in a PMA amendment. The final labeling describes the use of dual antiplatelet therapy in the ENDEAVOR trials and further states that "Current guidelines recommend that patients receive aspirin indefinitely and that clopidogrel therapy be extended to 12 months in patients at low risk of bleeding (ref: ACC/AHA/SCAI PCI Practice Guidelines[3,4])."

Additionally, Medtronic has agreed to conduct or participate in a study that will develop clinical data to identify the optimal duration of dual antiplatelet therapy following percutaneous intervention with the Endeavor drug-eluting stent.

The applicant's manufacturing and sterilization facilities were inspected and found to be in compliance with relevant Quality System Regulations (21 CFR 820) and pharmaceutical current Good Manufacturing Practice (cGMP) regulations.

FDA issued an approval order on February 1, 2008.

XV. Approved Specifications

Directions for Use: See product labeling.

Hazard to Health from Use of the Product: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Post Approval Requirements and Restrictions: See Approval Order.

XVI. References

[1] Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circ 2007;115:2344-51.

[2] Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0 – 30 days) will be used in the remainder of this document.

[3] Smith et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. JACC, 2006; 47: e1-121.

[4] King III et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. JACC, 2008; 51:172-209.